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ABSTRACT

This reports a conference of psychologists, psychiatrists, geneticists and others concerned with the biological and psychological effects of lysergic acid diethylamide and other hallucinogenic drugs. Clinical data are presented on adverse drug reactions. The difficulty of determining the causes of adverse reactions is discussed, as are different methods of therapy. Data are also presented on the psychological and physiological effects of L.S.D. given as a treatment under controlled medical conditions. Possible genetic effects of L.S.D. and other drugs are discussed on the basis of data from laboratory animals and humans. Also discussed are needs for futher research. The necessity to aviod scare techniques in disseminating information about drugs is emphasized. An appendix includes seven background papers reprinted from professional journals, and a bibliography of current articles on the possible genetic effects of drugs. (EB)

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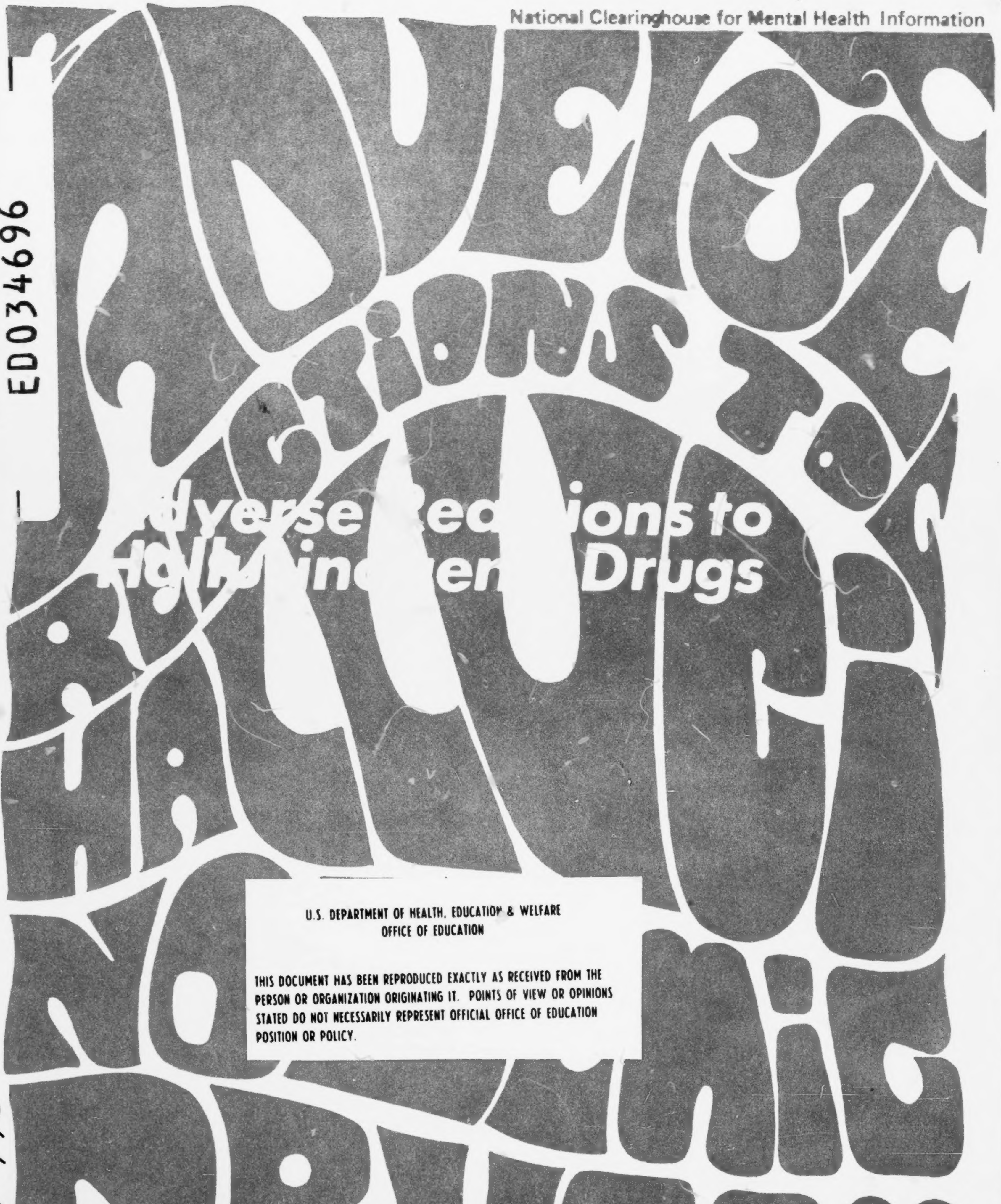

# Adverse Reactions to Hallucinogenic Drugs

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NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

# ADVERSE REACTIONS TO HALLUCINOGENIC DRUGS

## with Background Papers

Conference Held at the National Institute of Mental Health
Chevy Chase, Maryland, September 29, 1967

Roger E. Meyer, M.D., Editor

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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# Foreword

The National Institute of Mental Health through its Center for Studies of Narcotic and Drug Abuse serves as the focal point for support of research into the problems of drug abuse. The growing problem of hallucinogenic drug usage has been of great concern to the staff of this Center. In the midst of reports of the spreading epidemic of drug misuse and its sequelae, the National Institute of Mental Health has sought to clarify the many questions and myths that have arisen in both the lay and scientific press.

Consistent with this effort, the Center for Studies of Narcotic and Drug Abuse sponsored a meeting of scientists in September 1967 to discuss the psychological and biological sequelae of LSD use. This volume consists of the proceedings of that meeting, plus significant background papers which were available to the participants in advance of the meeting. While few definitive answers emerged from the discussions, the major questions were clearly defined and some research strategies were proposed. This book, in a way, serves as a bench mark of our knowledge at that time. The geneticists were as keenly interested in the deliberations of the psychiatrists and psychologists as the latter were intrigued by the findings of the former.

Subsequent to the meeting, the efforts of a number of people were responsible for its preparation in readable form. Miss Arlene Jaffe and Miss Eleanor Carroll, of the Center for Studies of Narcotic and Drug Abuse, and Miss Marilyn Wilhelms of the Office of Communications, NIMH, greatly assisted in the editing of the manuscript.

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# Introduction

**Dr. Roger Meyer:** On behalf of Dr. Yolles, I would like to welcome you to the National Institute of Mental Health and to thank you in advance for your participation today. A number of representatives of the Institute are present today—underlining our tremendous interest in your deliberations. Dr. Louis Wienckowski, Director, Division of Extramural Research; Dr. Sherman Kieffer, Director, National Center for Mental Health Services, Training and Research; Dr. Jerome Levine, Chief, Psychopharmacology Research Branch; and Dr. Morton Miller, Director, Division of Special Mental Health Programs are seated in various parts of the room. Before assuming my role as "David Susskind for a Day," I'd like to call upon Dr. Miller for some additional words of welcome.

**Dr. Morton Miller:** Speaking both for myself and the Director of the Institute, Dr. Yolles, and for the members of our National Advisory Mental Health Council, who have expressed extreme interest in this meeting, I would very much like to welcome you here. I was most impressed to see how many of you interrupted your very busy schedules to come to the meeting today, and I think it indeed reflects the concern of all of us about a very critical topic.

Just a few comments about what we consider to be the major significance of this particular meeting. It has been obvious that there has been a tremendous amount of interest nationally, both scientifically and politically, in the whole area of hallucinogenic drugs, with particular reference to the question of adverse effects, both short and long term, associated with LSD. This meeting, I think, is a very important step for us in the Division, particularly in the Center for Studies of Narcotic and Drug Abuse. We hope to define the current state of the art here today and to utilize your ideas and suggestions as a base for increasing our own efforts in the development of research and intervention programs in the area of hallucinogenic drug abuse. Again, I want to thank you very much for coming. This is a key conference, and I'm very pleased that I have a chance to spend at least some time with you today.

**Dr. Meyer:** Broadly speaking, our format today is almost pseudo-Lamarckian, that is, we shall be talking about a behavioral disorder that may have genetic implications. I would like to draw your attention to a letter we received from Dr. Morton Reiser [1] which was one of the stimuli for this meeting. Dr. Reiser expressed concern about possible toxic sequelae of LSD usage on the central nervous system. In particular, he was troubled by atypical psychotic reactions in some of his patients. These people did not appear to be schizophrenic (as defined in the traditional nomenclature) and he was alarmed about the possibility of an epidemic of heretofore undescribed organic brain syndromes.

The possible genetic implications of LSD abuse caused us to widen our format subsequent to the publication of Dr. Cohen's article in *Science*.[2] I hope that the format today, a round table discussion, will give you the freedom to discuss your findings, both current and past, very freely. We are taping the material because we've had such a demand to attend the conference that we've had to turn people away. We plan, therefore, to reproduce the proceedings.

This morning we shall be addressing ourselves to the psychological and behavioral problems associated with the use of LSD and other hallucinogenic drugs. I think that we have to define what the problem of LSD is now; to distinguish between the findings about LSD in the laboratory compared with its use in less formal surroundings. In other words, are adverse reactions clearly related to the setting in which the drug is administered? The reports of Drs. Smith, Frosch, Ungerleider, Wynne, and Silverman on illicit users of hallucinogens should be compared with some of the earlier reports of Drs. Osmond, Ditman, Freedman, and Shagass in various experimental studies.

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[1] Professor of Psychiatry, Albert Einstein College of Medicine, New York, New York.

[2] Cohen, M.M.; Marinello, M.J.; and Back, N. Chromosome damage in human leukocytes induced by Lysergic Acid Diethylamide. *Science*, 155:1417–1419, March 17, 1967.

Dr. Frosch has delineated three general psychological syndromes—the "bad" trips, the recurrent experiences, and the chronic psychoses. Others have listed suicide and chronic anxiety states as special syndromes secondary to LSD. Dr. Smith from San Francisco indicated his feeling that the drug might be implicated in the genesis of dysphoric feeling states that are being observed among some of the hippies. Again, Dr. Reiser's letter is fairly specific. He asks whether adverse reactions are not new syndromes, whether they are in fact toxic sequelae of the drug effects on the central nervous system. He feels they are not schizophrenic reactions and that most patients seem inaccessible to ordinary treatment. He also wonders whether the syndromes of black-market patients are different from those seen in controlled settings. One of the questions we would ask Dr. Joffe, from the Bureau of Narcotics and Dangerous Drugs, is whether contaminants are to be implicated in some of these syndromes that are being observed in the street? Can we better describe the reactions that are being observed in the street, or are we really limited to the three descriptive states that Dr. Frosch delineated in one of his earlier papers? What research strategies need to be pursued to further understand the problem? What stances are available to the Center, in research, and in professional, and preventive education? Finally, can this group make a start toward systemization of what is known while giving directions for the future? As a start I think I'd like to pass to Dr. Freedman.

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**Dr. Daniel Freedman:** The view that I've taken is one advocating caution as to how we interpret and talk about adverse drug reactions because I think it's really a problem of clinical psychiatry and clinical description. We have a great deal of sorting out to do with these drug reactions.

It's been my view as I've watched abuse develop over the past five or six years that there's very little hope that when most psychiatrists have their first contact with this drug they are going to be particularly sensible about viewing the phenomena induced by LSD. The same problem has occurred each time we've encountered any intense fluid mental state. Look at the way we've dealt with schizophrenia or hypnosis; it has taken time to sort out the details and it's going to take us time here, especially in the area of adverse reactions.

The difficulty of deciphering these new syndromes is particularly complicated by the fact that they may present themselves in different social or social-psychiatric contexts. For example, emergency rooms differ. The college campus differs from the city hospital. On the campus, the clinician has a greater potential for understanding the youngster who is in trouble and, knowing about his environment, what preceded his drug taking, and what went on during the drug episode. It is essential to sort out the several facts from their sum. We also have to cope with psychedelic philosophy far more often than we have to deal with drug problems; at least that's been my experience.

Aside from the questions of somatic changes which we are going to have to come to deal with, I think we have to recognize that the outcomes, at least of LSD use, are quite variable and we have to account for the variability. Despite this variability, many of the outcomes are quite predictable, and one could infer them from the multi-potential fluid mental state produced by the drug. I've tried to describe that from time to time but there's no question that the split of the self, that is, the entire experience of the self seeing the self, and the self seeing the self seeing, is an astonishing experience. It can also be a banal one. How could Heinrich Klüver give mescaline for years and never have a freak-out or even the intimation of a freak-out?[3] When I asked him, he said, "Because during the drug state we paid attention to what's 'out there.'" *The ability to hang on to stable, familiar anchors and clues is crucial.*

I have for a couple of years now been talking with some of the people in the Native American

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[3] Heinrich Klüver, Ph.D.—One of the most distinguished experimental biological psychologists and one of the earliest investigators in the field of hallucinogenic drugs with the publication of his monograph in 1928 entitled "Mescal, the 'Divine' Plant and Its Psychological Effects." Professor of Biological Psychology (Emeritus; Sewell L. Avery Distinguished Service Professor, University of Chicago).

Church. A resident, Dr. Robert Bergman, who was at the University of Chicago, has been working in the Public Health Service out there and has made a lot of observations. If we really take the Indian experience seriously it's useful because, in another psychosocial context, we have reports of drug-linked psychotic episodes that are generally brief and self-terminating. They have said that the persons who have these are generally pretty upset people to start with—people who have been psychotic.

I have a letter from Dr. Bergman reporting a "bad"trip of an Indian on mescaline; the reasons for it seemed to be that this fellow had a lot of problems that he wasn't sharing with the group before he took the drug, and yet it was a self-terminating experience. This raises the issue of what kind of problems a person does get into if he pays inordinate attention to what's "in here." *The real danger of LSD is that the wrong people seem to be taking it at the wrong time and for the wrong purposes.*

While I think I could make a case in terms of psychodynamic and psychological reasons alone as to why some adverse reactions would occur, I am aware that some of the syndromes we've seen look like something's wrong with the brain. I would, however, point again to the fact that there are no data. Ross Adey observed EEG changes in the cat for several weeks after LSD, but that cat had been trained to avoid electric shock.[4] The changes did not occur if the cat was not so trained. Thus the data do not mean that there is hippocampal "damage." They may mean that there are changes in brain waves that go along with changes in experience or in learning. Reserpine—with or without painful experiences—causes longer-term changes in the cat hippocampus, and we weren't told that we have to be wary of this drug because it causes brain damage.

Thus, while we look for somatic sequelae of LSD usage it is important to look for possible psychological or psychodynamic *precedents.* For example, I have no difficulty recognizing traumatic neurosis in those people I've seen who have trips without the drug. I do, however, have a lot of difficulty in figuring out why this repetitive behavior can occur under banal as well as disturbing circumstances.

I give the example of the scientist who simply could not suppress his peripheral vision for several months; he couldn't read his *London Times* as he was commuting because the telephone poles flashing by the train window bothered him. He lost the normal suppression of peripheral input. Well, that didn't seem to bother him too much. I've known people who are functioning well who have had macropsia and micropsia without LSD. It seems that there is a range of ways in which we normally habituate and relate fluidity and constancy in our perceptual behavior which these drug reactions should be making us think about.

I don't know what the barrier is—or what the switch is—between dereistic and reality thinking, but LSD and some of the events occurring under its influence make you think we haven't been focusing on that particular mechanism enough, namely, how to switch on and off two orders of reality. Having watched some of these things evolve over time, there's no question in my mind that the two orders of reality (Freud called them "the two principles of mental functioning") revealed by this drug—and known to man in many different forms for a long time—are hard to live with.

I'm trying to say that in behavior there's a dimension we'll call portentousness, by which I mean the capacity of the mind to have a psychedelic experience. Portentousness taps part of our experience—we see more than we can tell and experience more than we can explicate; we experience boundlessness as well as boundaries. Of this we're all quite capable. And we have symbolism for it; we speak of the cosmic, the endless, the infinite. I've been struck by the fact that when somebody takes this drug, he is so impressed by the two orders of reality—or the fact that this can happen—that he's at least puzzled and may be confused. It takes a lot of time to integrate the experience afterwards.

With regard to reports of birth defects and chromosomal abnormalities, I think it important to initiate a study of native American Indian groups having long histories of hallucinogenic drug use. At the present time, however, we don't know of any psychedelic monsters being born into these native cults. We need a good public health survey (including still-births and fertility) of these people, although I suspect that any suspicious trend would have struck the local enemies of peyote who've not picked up that objection to their neighbors' habits. In any case, I don't know of any problems that imply chromosomal change among these groups or any other native groups taking the drug. Accordingly, I come here prepared with a certain kind of skepticism about some of the basic science and laboratory indications that there are somatic dangers to LSD. I also come prepared as a physician, as I suppose most of us do, to believe that *any* drug can be harmful. It will take time to sort these things out.

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[4] Adey, W.R.; Porter, R.; and Walter, D.O. Prolonged effects of LSD on EEG records during discrimination performance in cats; evaluation by computer analysis. *Electroencephalography and Clinical Neurophysiology,* 18:25–35, January 1965.

I also come equipped with a deep wish that there would be a dire somatic consequence of the drug, because then we wouldn't have to spend all our time meeting about it, talking about it to parents, teachers, clubs, churches. My social life has changed a good deal due to the accident that I happened to study LSD ten years ago. Given this kind of skepticism, I've looked over the somatic data and the only thing I can conclude from looking at the rat and mouse data on still births is that if you're a prudent woman and yet you're going to take LSD, you either ought to be a confirmed virgin or on the pill.

I've been confronted from high quarters with the question: "How come my child, who was doing so well at college, is now a drop-out?" I've been confronted with that, however, in 1952, 1955, 1957, 1960, and 1964. I really am not sure, therefore, whether some very bright people (who are exposed to the drug) would indeed drop out without the aid of drugs. In other words, I don't know what's concomitant, precipitant, accidental, incidental, or whatever. I'm not convinced that we have any more problems with borderline states, adolescent turmoil, or the inability to meet the next life crisis than we have ever had. I have no question that the drug can reinforce any behavior pattern the person wishes or needs to adopt, but in assessing outcome we'll have to sort out what was before the trip. It is important to consider some of this: to remember that there are different motives for trying a drug, for interpreting its subjective effects, for maintaining the intake of a drug, for either taking it irresponsibly or ritually, for regulating its usage, and for stopping it.

As a start, I urge that a project that I proposed to Robert Cohen about three or four years ago now be implemented. This would involve a follow-up of the volunteers at NIMH who had LSD in 1952 or 1953.[5] I worked with a group of about ten for a year. These were well-screened people in many ways; I knew of no truly bad after-effects.

We have to understand why bad after-effects don't happen in order to understand better why we are ascribing certain causative factors to the adverse reaction. This is the reason for trying to map out what we can about the nature of the experience, its immediate after-effects, and its longer-term after-effects. How are they related? Obviously, prior set before a trip (or you might even call it the trip before the trip)—what a kid is going after, where he happened to be moving in life as he went into drug taking—are important factors to tease apart. Expectation—both conscious and unconscious—as well as guidance during a trip are important.

Finally, even if we patiently tease out the psychological and environmental factors, we may find that we are dealing sometimes with toxic psychoses. If we find this is to be true, we'll still have to distinguish the "bad" trip from all the other various outcomes, including "good" ones. We'll also have to remember that panic always "looks" organic. Homosexual panic often, at its height, shows organic features and makes you think something organic is going on. I think we ought to remember Weinstein and Kahn's approach to this problem.[6] In other words, I'd urge us, in teasing this apart, to try to be skeptical clinical psychologists and psychiatrists until we can begin to order the phenomena. So far as I'm concerned the people whom I have seen who have real trouble over a long period of time were headed there.

I'd like to know now what the usual time period is for the usual adverse reaction and that —in part—will depend on what the hospital is doing. If you haul a kid in panic to a state hospital, you've got a person in flux in whom you're reinforcing a break! If you've got a kid in panic and you calm him down and you don't make a "case" out of him, he may, with a few questions and follow-up over the next couple of weeks, be perfectly all right. Even with *no* follow-up, he may be all right.

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[5] Volunteers belonged to a small religious group which does not permit its members to smoke or drink.

[6] Weinstein, E.A., and Kahn, R.L. *Denial of Illness: Symbolic and Psychophysiological Aspects.* Springfield, Illinois: Charles C Thomas, 1955.

In other words, if you've got a person in a fluid state, how you reinforce that state may make a great deal of difference, and it's my impression that we had many more "bad" trips called to our attention after all of the panic publicity. I'd like to see a social-psychological study of newspaper articles and publicity and incidence. I think you will find that incidence follows publicity.

Well, this is just a range of problems. In a sense, they are of basic interest to this Institute, not simply because you are interested in the public health issue, but also because it is a beautiful challenge to tease apart those social, psychological, and biological variables which must be operating in any kind of behavior dysfunction.

**Dr. Meyer:** Do you know what dose they were given back in 1952?

**Dr. Freedman:** Yes, they were given various dosages, from 50 to 150 micrograms, as I recall.

**Dr. Wynne:** 150 is pretty standard dosage.

**Dr. Freedman:** They had patients and also volunteers that were treated. These volunteers got intravenous LSD (which gave them a more intense experience but in a highly comfortable setup). I didn't know then about all the beads and pads and so forth, but the research nurse and I would sit there and drink coffee while they performed various psychological tests for us from time to time. They got the drug at least once every ten days because I was studying acute and chronic tolerance. These people did come to new conclusions about their life, as any young kids would have done had they sat around in the cancer ward for a year volunteering their services. I think they were interested in the drug, but they were not entranced.

I saw one bad reaction. The youngster had the drug and went into a catatonic posture. He later said he heard himself giggle and thought he giggled "like a girl." That scared him. He in fact was young and somewhat immature and beardless. He stayed in this posture a few hours and we just worked with him until he came out of it. We talked with him over the next weeks and did not give him any more drugs. Six months later, he came back and said he had been looking out of his window at home and suddenly it was like the drug state; he wondered what that meant. We talked more about it and worked with him until we felt he was in fairly good charge of himself, and that was all of the problem that he had. This adverse trip and flashback was unanticipated. He had been thoroughly screened. All I can say is that he was immature. I then began to prefer counterphobic people who had at least been drunk once in their lives—who with favorable circumstances could sustain an altered state—and who had firm habits on which to rely. The chief issue is to know how to reinforce people during the trip.

**Dr. Meyer:** Thank you. Dr. Ungerleider will be our next speaker.

**Dr. Thomas Ungerleider:** Dr. Meyer asked for some scientific objectivity in this meeting today, but as far as I am concerned the words LSD and scientific objectivity are mutually exclusive, at least at this time. I would like to address some comments to this. I think we would all agree that LSD is a powerful chemical agent. Perhaps we would also agree that LSD can be abused under certain circumstances. Beyond that, I doubt that we would find much, if anything, that we here can all agree upon concerning the LSD situation today.

Some of you may agree with the New York Academy of Medicine that LSD is more dangerous than heroin. Perhaps some of you would agree with the superintendent of the California school system who stated recently that the use of LSD is the most critical problem in California's schools today. On the other hand, I have heard some of you say publicly that "anyone who can hold his alcohol can hold his LSD," and that "the chromosome problem is all due to the *fear* that adults have because LSD causes young people to become more artistic. They don't want to work from eight to five at the boring jobs which adults want everybody to hold."

Can we even agree on what *is* an adverse reaction to LSD? For example, at the last American Psychiatric Association meeting in May 1967, in Detroit, a foreign psychiatrist, who has made notable contributions in LSD therapy, claimed to have given patients up to 30 LSD treatments without observing any side effects. When my colleague, Dr. Fisher, later questioned him, the researcher admitted that some of his patients did become *psychotic* and others became *suicidal* and required hospitalization, but he insisted that these were *not* side effects but just part of "working through the LSD experience." He even regarded *convulsions* with tonic-clonic movements and loss of consciousness as part of the abreactive experience under LSD and not as a side effect of the drug.

Some of you share the opinion that even extensive LSD and other drug use in certain sections of various cities is *not* a problem of drug abuse but merely represents an eloquent protest of our youth to such social problems as Viet Nam, civil rights, and the like. Other physicians have informed me with equal sincerity that *all* LSD use is a giant Communist plot which is perpetrated by U. S. radio stations which play various songs such as "Acapulco Gold," and "Eight Miles High."

Such lack of basic agreement results in a climate of hysteria which has its unfortunate effects on all of us and on our studies. Certainly those of you who have used LSD in research and treatment have been especially affected. For example, the one pharmaceutical company with the experience and the equipment to analyze LSD samples has refused to analyze my (black market) samples out of fear of reprisals from the Government, particularly our own Food and Drug Administration. And representatives of another drug company, which manufactures a tranquilizer used to combat LSD-induced side effects, recently approached me to arrange a panel on the treatment of such reactions. They soon withdrew their offer, again because of difficulty with Federal agencies. The representatives of the company had told me that they were being bombarded with requests from physicians all over the country about choice of tranquilizers and dosage schedules to use in treating LSD reactions. They added that these requests would have to continue to be answered with a "no comment" type of statement. Whether their fears are justified or unjustified is not the point. The point is that with such rampant fear, many worthwhile projects are being abandoned, and LSD research faces a dismal future.

Now, can we define the "bad" trip, "bummer," or "freak-out" following LSD ingestion? I would say yes, or at least sometimes. My definition of an adverse reaction to LSD is this: "Symptoms following LSD ingestion which cause a person to seek professional help." There is precedent for such a definition. In the book, *The Psychiatric Emergency,*[7] a psychiatric emergency is defined thus: "All patients whose conditions warrant prompt psychiatric attention for whatever reason are designated emergencies."

Let me hasten to add that persons often seek help in indirect ways. When taking careful histories of those persons who come into our emergency rooms for help following LSD ingestion, we often find that these youngsters have been living nomadic lives away from their families. When they begin to have adverse effects from LSD, however, they find their way, often hundreds of miles, home to their parents. They know that their parents, being very "straight" and "up-tight," will immediately seek aid for them. Yet these youngsters, when brought in for help by their parents, will often say, "I'm only here at my parents' request." They can get help and still "save face" that way. It is surprising how readily they consent to and are relieved by psychiatric hospitalization.

At UCLA's Neuropsychiatric Institute, in the seven months beginning in September 1965, the first 70 cases of adverse effects from LSD were studied. The results have been detailed in a publication entitled, "The Dangers of LSD" in the *Journal of the American Medical Association.*[8] The predominant symptoms of these patients were hallucinations followed by anxiety, depression, and confusion, in decreasing order. The word hallucination is used loosely and also includes illusory phenomena. Lest any of you be surprised that confusion follows LSD ingestion (and some of you have expressed surprise to me in the past), let me refer you to an article by Dr. John MacDonald in the *American Journal of Psychiatry.*[9] He reports the experimental administration of LSD to 50 persons. Of the 50, 29 had some clouding of consciousness which varied from intermittent slight confusion to stupor.

During the time that our first 70 patients were seen at UCLA, for every person seen we received an additional three or four telephone calls from other people in trouble from LSD who did *not* subsequently come in for help. Since that time, at UCLA we have actively tried to *discourage*

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[7] Glasscote, R.M., et al. *The Psychiatric Emergency.* Joint Information Service of the American Psychiatric Association and the National Association for Mental Health, Washington, D.C., 1966.

[8] Ungerleider, J. T., et al. The dangers of LSD. *JAMA,* 197:389–392, August 8, 1966.

[9] MacDonald, J.M., and Galvin, J.A.V. Experimental psychotic states. *American Journal of Psychiatry,* 112:970–976, June 1956.

LSD patients from coming to our Neuropsychiatric Institute. In fact, for the first time since our Institute opened, a blanket rule was passed that a certain type of patient would not be hospitalized, namely, LSD patients. This is necessary because UCLA is a residency training hospital, and the psychiatric residents were seeing mainly one type of patient, the LSD casualty. Despite active discouragement, since April 1966 another 115 patients whose symptoms were directly related to LSD ingestion have been seen at the Neuropsychiatric Institute's Emergency Room. This figure excludes those patients who had used LSD in the remote past and whose presenting symptoms did not appear related to the LSD ingestion. (Some "flashback" re-creations of previous LSD trips have been included in the figures.) The figure also excludes a number of paranoid schizophrenics who claimed to have been poisoned by LSD, by the Communists or others, but who had little likelihood of exposure to the drug. It further excludes the multiple telephone calls and referrals (from five to ten each week day) that Dr. Fisher and I receive directly from the community which do not go through the Emergency Room.

It is important to emphasize that the symptoms I have described, namely, hallucinations, anxiety, depression, and confusion, frequently are experienced following the ingestion of LSD. These acute effects only come to be called side effects or an adverse reaction when the user seeks help for them. Many and perhaps most LSD users experience some or all of these effects but they are able to get over them, either by themselves (often with various aids such as readings from the *Tibetan Book of the Dead*) or with the help of a sitter or guide. We do not say then that these users are having adverse LSD reactions.

I am excluding many of the chronic changes due to LSD in my definition of the "bad" trip. Dr. Fisher and I left the hospital environment early to observe "love-ins, love sessions, and happenings" involving LSD throughout the State of California. These have included serious religious rites in the Orange County Southern California area, as well as our local Sunset Strip and Hollywood kick-type parties, hippies "dropping acid" at Big Sur, and college students experimenting in the San Francisco Bay Area. We have seen many persons on LSD who appeared grossly psychotic. I personally have seen several Virgin Marys wandering about on LSD, but either their culture supported them or they were not aware of enough difficulty to seek aid. I would therefore exclude them from our definition of adverse reactions to LSD. This also avoids the controversy about value-system changes with people "turning on" with LSD and then dropping out of society as we know it.

Unfortunately, we do not know and probably will never know the true prevalence of LSD usage in the community. We do not even know the incidence of "bad" trips seen in hospitals and by professionals because few statistics exist. We are now beginning a questionnaire survey of professional persons in Los Angeles County to try to determine how many adverse LSD reactions they have seen in the 18-month period ending this past July.

Much controversy has arisen as to whether pure LSD causes adverse effects or whether it is the black-market LSD with its alleged impurities and dosage irregularities. I have had several samples spot-checked and analyzed and, in each sample, where the user claimed he was getting LSD he always was. These users were chronic "acid heads," who claimed they could tell within 5 micrograms how much LSD they were ingesting. There were no impurities or other drugs found in these few samples, but the user always thought he was taking much more LSD than he really was.

We professionals often debate the *etiology* of the adverse LSD reaction as well as the *definition of it*. Is it the *impure LSD* with methedrine or atropine derivatives that causes the adverse reactions? I personally don't think so. Is it set and setting with whimsical or kick-type parties that are responsible for most of the "bad" trips? I don't think so. In fact I am more impressed with the set and setting of many of the serious black-market users than I am with the often sterile medical atmosphere and environment in which we have given the pure Sandoz LSD. Is the adverse LSD reaction to be explained by *psychopathology* in the user who is borderline or emotionally ill anyway? I am most unimpressed with this factor. Certainly, existing screening techniques have failed to rule out a number of adverse reactors while many very disturbed persons take LSD in huge doses multiple times, without apparent adverse effects.

I would however like to suggest one factor which I do not feel has received enough emphasis and which may help us to resolve our apparent disagreements about the dangers of LSD. The average age of the user in our study of the adverse reactor to LSD was 21. In other studies the age has been reported as the same or even younger. We all know that adolescence is a time of instinctual crisis with youngsters trying to handle their sexual and aggressive feelings and to resolve their identity problems. I am convinced that using LSD makes this resolution much more difficult, both in the chronic "acid head" and in the occasional LSD user. The "anti-instinctual" properties of the drug give the LSD user the *illusion* that he has no sexual or angry conflicts. He can thus postpone or avoid conflict resolution for many months, while he "turns on."

To my knowledge, virtually all of the work that has been done in both therapy and research with LSD has been done in subjects over 21 years of age. Perhaps, then, the age—or youth—of the black-market users explains many of the adverse reactions to LSD. Certainly Drs. Sidney Cohen, Ditman, and Grof, to name a few, have only very rarely administered LSD to persons under 21. I am aware, however, that paranoid personalities, very compulsive persons, and some others in the older age groups have had adverse reactions to the drug.

**Dr. Meyer:** Thank you very much. I am certain that Dr. Joffe, representing the Bureau of Narcotics and Dangerous Drugs, might want to respond to some of your comments about Federal regulatory agencies.

**Dr. Milton Joffe:** I'm rather glad that Dr. Meyer suggested that I answer some of these comments because I wanted to answer them anyway. As to the Government's role in regulation of this compound, I think it has changed markedly in the last year. I wanted to comment that Dr. Freedman and Dr. Osmond, in their prepared statements, had been writing in 1966, some months before those of us who are scientific people were in the Bureau of Narcotics and Dangerous Drugs in the Food and Drug Administration.[10] I might say that their statements are now rather outdated, that there is a Joint FDA-PHS Psychotomimetic Agents Advisory Committee which will approve the use of psychedelic drugs and provide for their supply. Anyone of you can reach this committee through Dr. Scigliano, Center for Studies of Narcotic and Drug Abuse, NIMH.

As far as the quotation from Dr. Freedman that "fear of sensationalism in the bureaucracy due to the sanction of drug abuse" is concerned, he has not dealt with the Division of Drug Sciences, Bureau of Narcotics and Dangerous Drugs, particularly with Dr. Richards, our social psychologist; Dr. Smith, our clinical psychologist; and myself, a pharmacologist. I think that he will find that we are not afraid to sanction the use of drugs in research. We are trying to assist scientific investigators in every way that we can. It is true we would like to avoid sensationalism. I think almost everyone would. We are a Government agency with a regulatory function and "a different outlook." Contrary to most government regulatory agencies we are also responsible for research to determine what the problem is about, what the extent of it is, and what might be done about it. We hope that we will be able to foster and *extend* this point of view.

As to observations about the illicit sources, I think if one wanted to know more about these, he should call on our criminal investigators. I can say just a few things about the illicit production from what I know; I do not make it a point to investigate or even to find out about all of the illegal laboratories that investigators turn up. The most common type of facility of this kind is the home-type laboratory where somebody in a rooming house sets up a window fan for exhausting organic vapors and employs unquantitative chemical procedures. Generally the discovery of the laboratory is made because in the same rooming house there are people who are not familiar with the odor of organic solvents and they call the police.

The product turned out by these laboratories is of course very questionable. The matter that Dr. Ungerleider brought up concerning the contaminants is a problem which we would certainly like to get into, but it would require more resources and more study than we can devote to it right now. We don't know whether the contaminants are due simply to residues from the chemical processing, a breakdown of the actual product, or an incomplete synthesis; the only thing we can tell is that the sample does not assay to be 100 percent.

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[10] This Bureau was originally under the Food and Drug Administration and is now part of the Justice Department.

In connection with this problem, I have had a call from one of the participants here who is on the negative side of the chromosomal-break investigation; his thought was that perhaps it was the contaminants rather than the pure material which were producing this break. While I am in a position to furnish him with illicit material, I cannot guarantee what the contaminants will be. A first step might be to determine whether pure LSD does not break chromosomes while the illicit stuff does. After this, one can look for identification of contaminants. Apart from the smaller household laboratories there are also some bigger processors that we have come across. One example was the laboratory truck found in Colorado whose owners had a rather high level of sophistication. There were xeroxed copies of all of Roger Adams' patents on the tetrahydrocannabinols, of John Biel's papers on the anticholinergics, and of course several reprints of Dr. Shulgin's work on the mescaline compounds.

We don't ever know what's going to turn up next. My own particular guess is that anticholinergics will not become a large problem. The reaction to them is rather unpleasant. I do not expect the illicit chemists' level of sophistication to be such that they will be able to synthesize tetrahydrocannabinols in any sizable quantity, at least, at present. I personally expect a flood of more phenylethylamines such as the DOM or STP.

These compounds are easily made. The literture on them is rather extensive, as far as synthesis goes. There are no tricks to it; it is a simple straightforward following of known chemical techniques. I also expect that the users will gravitate to these substances rather than seeking out the exotic or compounds unknown today. I don't expect the illicit chemists to go about and synthesize or carry out research on any *new* series of compounds. There is certainly the possibility of the synthesis of the tetrahydrocannabinols since Mechoulam's publication of a rather easy synthesis. Here the problem for the investigator is the purchase of starting materials and the development of a synthesis capable of generating significant quantities of the substance. At this point in time, it is easier for the illicit chemist to prepare THC from the plant.

In reality, the main problem that we are facing on a long-range basis is that of LSD. It is extremely potent, with generally low toxicity, and I believe that it has a certain status in the subculture which the other drugs do not have. The unpredictability of the "good" versus the "bad" trip really puts the user on what the animal psychologist would call the "variable-ratio" or "gambler's schedule." You don't have to be reinforced each time, but if you get one or two reinforcements from "good" trips, the user will continue to use this material.

Another problem that we have had with compounds, mainly on the East rather than on the West Coast, has been with the indole compounds of dimethyltryptamine (DMT) and diethyltryptamine (DET). These are easily made. They are, of course, used by inhalation since they are inactive orally. And they are used in a peculiar way. It sometimes takes the police quite a while to catch on to the fact that the purchase they have made from illicit sources is not *obviously* illegal. They bring the material to the laboratory for analysis and are told, "You have been stuck this time because there's nothing here but parsley leaves." It turns out to be parsley leaves with the liquid DMT spiked on it and dried.

The techniques that the illicit sources will resort to are rather clever; and I'm sure it's going to be a problem for the enforcement people to keep ahead of them. From our standpoint of scientific investigation, we are obviously incapable of fostering every type of research that needs to be done. I think we would all be most receptive to proposals for work in this area. There are times, as I say, when we, partly because of our particular mission, will not be able to do anything about the problem. We certainly can offer you encouragement and advice concerning Government regulation. Our whole mission is to foster research, and we would be more than happy to try and help you wend your way through the bureaucracy. It's a problem not just for you, but it's a problem for me. There are other Government agencies which I am not a part of, and I have to wend my way through them.

I think that, in looking over what Dr. Smith has submitted concerning STP use, I might anticipate him just a little bit. I don't know what he's going to say in regard to the matter of treatment and the chlorpromazine issue. You will recall that there were reports from Dr. Smith's clinic that chlorpromazine potentiated STP, causing death in one individual, and suggesting that STP therefore acted like an anticholinergic substance rather than a phenylethylamine. I've not had the opportunity to talk directly with Dr. Smith about this report. I did, however, talk to his co-worker, Dr. Frederick Meyers, who was not sure about the findings of the initial report and the conclusions drawn from it.

I've recently had some experimental work run off in a human subject. The chlorpromazine was not given as antidotal treatment but rather was given simultaneously with the DOM, and the reaction of the individual was considerably less. This was an individual who had had a full-scale reaction to STP when chlorpromazine was not administered. His reaction was considerably diminished upon taking the chlorpromazine simultaneously.

The general thought of the man who did this work was that we were simply depressing the whole individual; there was nothing specific about it and perhaps the tranquilizers should be considered as some therapy for an individual who is in danger of becoming either violent or very panicky.

I don't think I have anything more to say except to reiterate that the Bureau of Narcotics and Dangerous Drugs is more than willing to discuss with anyone the problems involved in scientific investigation. I may say now that, even though the Government has the reputation for repressing research in the LSD area, there are at present over 100 individuals who are authorized legally to do scientific work with LSD and other psychedelics, and this number will increase, probably significantly, every two months as the special committee meets to approve these applications.

**Dr. Meyer:** Dr. Joffe, there has been one report that STP on the East Coast is different from that on the West Coast. Would you care to comment?

**Dr. Joffe:** We have had a small amount from the East Coast but most has been from the West Coast. There is an individual here who is responsible for providing me with the very first tablet on which our structure was established and I'm very grateful to him. This tablet, obtained from the New York area, was of a different color and size than the ones from the West Coast. The West Coast ones were blue-green, the New York one a beige color. This doesn't really mean too much because we don't know too much about the manufacture of them, but very simply, every tablet that our agents have been able to obtain or that I have been able to obtain from scientific people—every tablet which was said to be STP and contained a psychogenic compound—had only one compound in it, namely 2,5–dimethoxy–4–methylamphetamine. To my knowledge, there are no other psychogenic compounds circulating under the name of STP.

**Dr. Meyer:** Dr. Freedman had one comment to make, I think.

**Dr. Freedman:** The source of my statement refers back to the Kennedy hearings, in which I had observed that what I meant by bureaucratic power was simply the option to make decisions. It is my feeling that it is difficult to make controversial decisions when a man has to face Congress.

**Dr. Joffe:** We are trying to hold up our end of it.

**Dr. Freedman:** Yes, I know.

**Dr. Smith:** Can I ask one question? On what do you base your conclusion that tetrahydrocannabinols (THC) will not become a problem?

**Dr. Joffe:** I would say that the present synthesis is relatively easy as compared with the original synthesis of Roger Adams, but it still does not represent an easy synthesis. As I said, the illegal sources provided us with a very nice series of xeroxed copies. If they are taking this literature seriously, are capable of understanding it, and have the facilities, it would not be beyond their powers to make it.

**Dr. Smith:** There have been reports of tetrahydrocannabinol circulating in the Haight-Ashbury.

**Dr. Joffe:** Can you get me a sample? I would be very glad to have a sample because there are really two compounds in one series and a whole flock of compounds in another series that we have to worry about. The two compounds in the one series are the L-$\Delta^9$-trans-THC, the L-$\Delta^8$-trans-THC. There are compounds which can be isolated from the plant. They are also synthesizable and have been tested in man. The other series of compounds is based on the delta 3, 4 tetrahydrocannabinols which are Roger Adams' compounds. Furthermore, since the substitutions of R–3 can be of an almost infinite variety, we have here at least a potential for a great many compounds. A number of them have been made including synhexyl, synheptal, and ones with an even longer chain which have a higher potency. I don't ask Dr. Smith for a sample out of idle curiosity. I would certainly like to determine whether this synthetic material is made by Mechoulam's synthesis which would give the L-trans delta 1 or whether it is made from the Roger Adams' series which would be the delta 3, 4.

**Dr. Meyer:** Thank you. I'd like now to call on Dr. Shagass.

**Dr. Charles Shagass:** What I have to say this morning is a background to what Dr. Hungerford is going to be saying this afternoon about our chromosome study. I have had various kinds of interest in LSD. I started giving it in 1950 to try to produce abreactions in therapy, and for the next decade I continued to give it sporadically. I was very unimpressed by the effects and wondered why the literature was so full of statements which my observations failed to confirm. I was probably not giving enough LSD, and was giving it to the wrong people; my patients were people who didn't display psychotomimetic effects with small doses.

Another interest was whether the LSD reaction resembles schizophrenia. Most people don't believe this anymore, and in fact, there is a good deal of evidence from various sources to support the notion that the psychotomimetic effects are toxic. For instance, if you give the Bender-Gestalt test, the people who show the greatest clinical reaction to LSD are those who have deterioration of performance. On the other hand, LSD, as we showed in another study, is quite different from an agent like Ditran, which is a deliriant. If you take a group of subjects and give them a performance test, and then test them when they are under the influence of the agent, the performance level is maintained under LSD. There is a significant correlation between the pre- and post-drug scores. On the other hand, with Ditran, the performance level is completely lost; you can't predict what the drug performance is going to be from the pre-testing. So LSD is certainly not as toxic an agent in that sense as Ditran. There are other differences electrophysiologically.

In 1963 we again became interested in the issue of treatment with LSD. This time we set out to determine whether we could predict clinically who would have a so-called psychedelic experience (Dr. Osmond's term) or insightful experience, or whatever you want to call it. We loaded our group with conduct disorders; 10 of our first 20 subjects were court referred. They were first given a standardized psychiatric interview schedule for diagnostic classification. Our LSD treatment method was of the kind that has been used in the treatment of alcoholism; the dose was 2.5 micrograms per kilo given intravenously, which is a large dose in terms of its effects.

Two psychiatrists rated the taped records of the experience for the presence and degree of insightful response. Thus we were able to divide our group roughly into two segments: those with more evidence of insight—responders, and those with little or no insight—nonresponders. It turned out that most of our responders had been diagnosed as psychopathic personalities by our interview schedule. Furthermore, no responder was under 22 years old. Parenthetically, we have never seen what we would call a favorable therapeutic response to LSD in anybody under 22. Thus, on the basis of age and personality there was a way of selecting in advance those capable of having an immediate insightful response to LSD. The group was a mixed bag of alcoholics, homosexuals, exhibitionists, and dexedrine takers.

We then did a follow-up study. Each patient to be treated with LSD was described (i.e. symptoms) in advance. From the records we found another patient of the same age, sex, symptom pattern, and socio-economic status. After one year we sought out these individuals, both the LSD-treated patients and their controls, and interviewed them and a significant relative.

Each symptom was inquired into and, if they said there had been a change, they were asked to rate the degree of change on a rough scale. Although our matching for symptom patterns was very close, we did not control for other treatments; it turned out that three of the LSD patients had had some regular psychotherapy, whereas 13 of the 20 control cases had been seen at least once weekly in psychotherapy during the one-year follow up. Mean ratings of improvement in symptoms were computed for six months after treatment (a retrospective rating) and at 12 months. The people given one 200 microgram, or 2.5 microgram per kilo, treatment with LSD showed significantly more improvement at both six and 12 months. Those who showed the greatest improvement were our eight responders; at six months they were very much improved, and then they started to show a tendency to relapse. The relapse had a remarkable time characteristic. Within seven months after taking LSD the individual started to want to consort with homosexuals again, to drink again, and so on. We have no idea why there is this six month improvement and then the tendency to relapse. It raises the question of a possible mechanism that is set off by the LSD which remains operative for this period of time.

Another finding that came out of this analysis, which may be a chance finding, although it is statistically significant, is that the change in the ratings from six to 12 months showed significant improvement only in the group of 12 LSD nonresponders. These people just seemed to keep on improving gradually. If this is a genuine phenomenon, what could be going on? Something of a long-term nature must have been triggered.

Concomitantly with treatment, we studied some electrophysiological changes in 17 of our subjects. We looked at the EEG and at the sensory-evoked responses to light flash and to electrical stimulation of the median nerve. Histograms showing the distribution of wave durations in the electroencephalogram were computed before LSD was given, at a time close to the height of the LSD effect, and then the next day. EEG frequency was generally increased by LSD, as other people have found. It is important to note, however, that one day later the frequency histogram was about the same as before LSD. It seems that these EEG effects don't last.

A paper in *JAMA*[11] last week, concerning brain damage by LSD in a five-year-old girl, states that there have been no long-term EEG studies of LSD. We have seen the EEG's of many patients a long time after they have had LSD; there are no changes evident after 24 hours. Similarly, the average evoked responses to light flash show some definite changes produced by LSD, but the records are pretty much back to the pre-drug form in one day. The same is true of the responses to median nerve stimulation.

The position that we had to take from our results is that, first of all, we do have evidence suggesting that LSD may produce therapeutic effects; although this is certainly not anything to get overly excited about as a specific procedure, since people do relapse. However, we have retreated some of the relapsers and produced another six months benefit. Secondly, the electrophysiological changes that we have been able to measure do not last beyond the acute phase. This is in accord with the notion that there is some kind of toxic reaction. The nature of this reaction is electrophysiologically interesting, in that we are seeing a *speeding up* of brain activity. Most toxic agents, such as the anticholinergics, of which Ditran is an example, *slow* brain activity. This is one of the few examples we have of the postulated parabolic relationship between performance and underlying physiological activity. At the extremes of physiological activity, which could be exemplified by panic and sleep, very little intelligent performance can occur. It has been extraordinarily difficult to obtain a physiological parallel at the panic level, although it is very easy to record the slow sleep activity. Now, what we have with LSD is a speeding up that is associated with decrement of performance, and this is of some interest.

Lastly, it seems to me that a lot of things that one sees in working with LSD suggest that this drug, or something like it, should be able to tell us a great deal about the basic structure of personality. Why does a sociopath, having had LSD once, say: "I will not come back for a second treatment, because when I had my first one, all it did was tell me that it was my fault."? Cognitively, he knew it was his fault before he ever had any LSD. Apparently the LSD made him know in an affective sense, and this was an experience to which he was not going to subject himself again. What kind of personality organization was shifted by LSD?

Because of these interests, after I moved to Philadelphia about a year and a half ago, we continued our work with LSD. We have been trying to block what I think is the major toxic phase of the LSD reaction, that taking place during the first four hours. We give patients a pill, which is either chlorpromazine or placebo, before giving the LSD. The blocking is of varying success; some people just don't block and go to sleep for 12 hours with chlorpromazine. In any case, our aim has been to compare blocked and unblocked treatments to see whether the initial three or four hours of what I believe to be toxicity is at all necessary for later behavioral change. We want to know whether the patient will have his insightful experience without having to be quasi-psychotic for awhile. This has been our purpose. Now, in connection with this, we were really only getting started when Dr. Cohen's report came out. I happened to be talking to a biologist at the time who suggested that I do something about this, and referred me to Dr. Hungerford. This was how we started to collect blood samples for chromosome studies in each patient, and that is the background for Dr. Hungerford's story.

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[11] Milman, D.H. An untoward reaction to accidental ingestion of LSD in a five-year-old girl. *JAMA*, 201(11):821–824, September 11, 1967.

One final small point I should like to make concerns reports of LSD dosage. In the *JAMA*[12] article of last week there appears to be uncritical acceptance of the statement that a sugar cube, impregnated with illicit LSD, which was swallowed by a five-year-old girl, contained a standard 100 microgram dose of LSD. How do they know the dose? It was an impregnated black-market sugar cube which an 18-year-old boy had put in the refrigerator.

**Dr. Freedman:** What has been your experience with "freak-outs" in the treatment situation?

**Dr. Shagass:** We have had three people become lastingly psychotic. I agree with Dr. Ungerleider that during the treatment session a "freak-out" is a very uncommon affair. However, when we were deliberately trying to produce a psychotic reaction, our yield was 50 percent. This was in a study we did in 1960.

**Dr. Freedman:** What is it you were trying to produce? You and I will have an argument later as to what psychosis is.

**Dr. Shagass:** What we were trying to produce at that time was something that would meet the clinical criteria of a psychotic reaction as these were defined in the standard APA nomenclature terms.

**Dr. Freedman:** Secondary or permanent?

**Dr. Shagass:** Secondary. In 14 patients to whom we gave several doses of LSD, we got seven immediate sudden reactions that were clearly clinical psychosis, but three of them, as I recall, were organic in the sense that there was disorientation. There was one clear case of catatonia. One man became sufficiently paranoid to try to kill the investigator. He was sorry about it later.

In our therapeutic context, our experience has been that people have a lot of symptoms that could be called psychotic, but these are quite well controlled. I didn't go into detail about the context. My view, and I go along with Dr. Freedman here, is that we have a very complex interaction when we try to use LSD for treatment. We have the expectancies of the patient; we have the expectancies of the therapist; we have this potent agent which heightens suggestibility; and we have the setting. I think all of these are necessary in order to produce some of these effects.

QUESTION: What dosage was it initially in studying psychosis?

**Dr. Shagass:** In another study using a group of 14, we went as high as 500 micrograms without success in producing what we call a psychotic reaction.

QUESTION: These included your alcoholics?

**Dr. Shagass:** No. This was an entirely different study. In our use of LSD as a therapeutic agent, we have used one of two doses: 2.5 micrograms per kilo or 200 micrograms, whichever is smaller. We gave it intravenously which, I am told, makes the effect of the drug two and one-half to three times more rapid in onset.

QUESTION: What was the dose that gave you up to 50 percent psychosis?

**Dr. Shagass:** This wasn't set, but we went from 2.5 to 9 micrograms per kilo in that study in an attempt to produce psychosis. What we were trying to do, you see, was to compare in the same person a psychotic and a non-psychotic reaction to LSD using different tests. This was done with Dan Pauk about 1961.[13]

QUESTION: Was the incidence of psychoses dose related?

**Dr. Shagass:** Yes. Certainly at one-half microgram per kilo you get a very low yield of anything.

I am distinguishing between a reaction to a drug which you get in nearly anybody to whom you give it at most dosage levels above a minimum, and a disorganized behavioral reaction which fits a syndrome picture. At that time we were very much concerned with the question of whether this was really an hallucinogenic drug, when actually the phenomena may have been il-

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[12] *Ibid.*

[13] Pauk, Z.D., and Shagass, C. Some test findings associated with susceptibility to psychosis induced by Lysergic Acid Diethylamide. *Comprehensive Psychiatry*, 2:188–195, August 1961.

lusions. The term psychotogenic is used and this implies the notion that the effects are like schizophrenia. These are reactions which involve serious departures from the organization of the mind in relation to what we ordinarily see. We started out by asking: Are they the same?
QUESTION: Your feeling is that they are the same?

**Dr. Shagass:** For the most part, yes. In the three patients that I have mentioned, we have seen the development of psychotic reactions which were clinically exactly like the schizophrenic syndromes that one sees in the absence of LSD. One schizophrenic reaction occurred in a man who had a prior history of a brief psychotic episode subsequent to leaving an isolated work area. This perhaps should have warned us, but we treated him because of his exhibitionism which had been refractory to psychiatric therapy and he did not appear overtly psychotic at the time. This patient developed a schizophrenic reaction after his fourth session with LSD. It started during the experience, and afterwards it required about two months of traditional treatment for recovery. The treatment was the same as for a schizophrenic reaction which has not been precipitated by LSD.

**Dr. Meyer:** Had these reactions been seen in people who had been previously unstable?

**Dr. Shagass:** Yes.

**Dr. Meyer:** You would feel that a psychological diathesis was there?

**Dr. Shagass:** Yes.
QUESTION: And these were the only persisting reactions?

**Dr. Shagass:** Yes. Of special interest was a man who came to us with a methedrine psychosis. He was also a former narcotic addict. The methedrine reaction cleared in three days and he appeared clinically in excellent contact and we decided to take a chance on him with LSD. He had a beautiful psychedelic experience, seemed to reorganize, became ambitious, and really looked marvelous. Yet 16 days after his fourth and last LSD experience, he became floridly paranoid and presented exactly the same picture as he did under the methedrine. This did not clear up until he was treated, as before (with the methedrine psychosis). On both occasions, he was very difficult to treat.

**Dr. Meyer:** To your knowledge, has anyone done any EEG studies of the so-called recurrent experiences without the LSD?

**Dr. Shagass:** No. I'm just a little skeptical about what this means. We recently gave LSD to a *Popular Science* writer who is a very anxious person. He now feels fine and he has written a very nice story about his experience for the magazine.[14] In talking to him later, he brought up the fact that he had an anxiety dream one night and said it was just like the LSD experience. Well, I think if I had focused on a previous experience that had some kind of dramatic context, I could have elicited a similar report before he ever got any LSD.

**Dr. Frosch:** We've done EEG's on some of the people whom we've labeled as recurrences. We found no encephalographic abnormalities. But of course, Dr. Shagass observed no electrocephalographic changes unless he did the computerized wave analysis.

**Dr. Meyer:** Thank you very much. I'd like to call on Dr. Silverman next.

**Dr. Julian Silverman:** I'm going to report on a study carried out in collaboration with Drs. Monte Buchsbaum, Winfield Scott, Douglas Welpton, Lyman Wynne, and Theodore Zahn of NIMH and Dr. Robert Henkin of NHI. The subjects in the study were eight male chronic LSD users who ranged in age between 21 and 33 years, average number of drug experiences—35; they were examined intensively every day for a week with an elaborate battery of physiological and psychological tests. Measures of sensory thresholds, perceptual functioning, EEG averaged cortical evoked responses, autonomic reactivity, and a battery of clinical psychological and personality tests were administered to each subject under four conditions: (a) baseline—day one, (b) with 15 mg. d-Amphetamine—day two, (c) with 50 micrograms of LSD-25—day four, (d) 24 hours after LSD day—day five. The baseline measurements made on these subjects were compared with those of 20 normal male volunteers of similar age. The overall significant effects of LSD will be reported, in detail, by Dr. Henkin at the Eastern meetings of the American Federation for Clinical Research in December 1967. Since the main emphasis of my talk is on individual differences in LSD reactions, I will only summarize briefly our general findings regarding LSD effects:

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[14] Gannon, R. My LSD trip: non-cop, non-hippie report. *Popular Science*, 191:60–65+, December 1967.

1. Auditory Thresholds, measured by a standard audiometric procedure, *were lower on baseline day* for LSD subjects than for non-drugged, non-psychiatric control subjects.

2. Following LSD ingestion, auditory thresholds were found to decrease even further in the majority of subjects (5) and not to change, but to remain low, in the other subjects. This finding is in accord with the sensory threshold results of other investigators who have taken special care to establish a *relaxed* and *cooperative* attitude on the part of their subjects (e.g., Roland Fischer, Ohio State Medical School). Dr. Henkin, who carried out the sensory threshold testing, was especially impressed with the performances of the LSD-drugged subjects. He compared them with patients with Addison's disease who are extraordinarily hypersensitive to low intensity stimulation when not treated with adrenal cortical hormone.

3. No significant changes were found in taste and smell thresholds under any condition.

4. Thresholds for "auditory discomfort" were found to be significantly *higher* than normal on baseline day and were increased further on LSD day. This finding is consistent with research reports of decreased sensitivity to pain under the influence of LSD.[15] The paradoxical positive correlation within the same subjects of increased sensitivity to low intensity stimulation and decreased sensitivity to high intensity stimulation, i.e., to pain, is considered in detail in a paper entitled "A Paradigm for the Study of Altered States of Consciousness," by J. Silverman.[16]

**Dr. Lyman Wynne:** Let me just underline that our subjects' chronic usage of LSD had been interrupted prior to their coming in for the study so that there wasn't any likelihood of an immediate toxic effect or other kind of effect from usage during the previous week.

**Dr. Silverman:**

5. On speech discrimination tests designed to measure auditory integration capacity, our subjects evidenced some deficit in auditory integration on baseline day and a highly significant integration deficit on LSD day. Other investigators have noted a positive correlation, within subjects, between unusually low sensory thresholds and deficient performance on tests of perceptual integration.[17] This relationship is found in both clinically normal and abnormal subjects.

6. Pupillary dilation measured after LSD was ingested was significantly greater than on any other testing occasion.

7. An interesting electroencephalographic effect was observed. Using a newly developed procedure for measuring cortical averaged evoked responses (to light flashes), four different intensities of stimulation were employed.[18] The amplitude and latency values of the averaged evoked responses (AER) were computed for different peaks of the AER Waveform. One (and only one) remarkable effect was noted on one peak of the AER Waveform which deserves to be elaborated upon. Briefly, among non-drug-user, non-psychiatric subjects, increasingly shorter averaged evoked response latencies are recorded as you increase the intensity of the photic stimuli. The slope of the stimulus intensity-AER latency function is linear and very steep for normal male subjects; that is, AER latencies are relatively long at the lowest stimulus intensity and very short at the highest stimulus intensity. (a) For our drug-user subjects, *on baseline day*, the stimulus intensity-latency function (slope) was significantly less steep than that for a group of normal male subjects. The average slope score was more similar to that of a group of normal female subjects. (It certainly is noteworthy that when sex differences are found on sensory threshold tests and perceptual integration tests, females evidence lower threshold and less efficient perceptual integration—similar to our male, LSD-user subjects. The difference in AER latency slope scores of normal males and normal females is highly significant.) (b) A couple

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[15] Kast, E., and Collins, V.J. Study of Lysergic Acid Diethylamide as an analgesic agent. *Anesthesia and Analgesia*, 43:285–291, May-June 1964.

[16] Silverman, J. A paradigm for the study of altered states of consciousness. *British Journal of Psychiatry*, 114:1201–1218, October 1968.

[17] Kaswan, J.; Haralson, S.; and Cline, R. Variables in perceptual and cognitive organization and differentiation. *Journal of Personality*, 33:164–177, June 1965.

[18] Buchsbaum, M., and Silverman, J. Stimulus intensity control and the cortical evoked response. *Psychosomatic Medicine*, 30:12–22, January-February 1968.

of hours after ingestion of 50 micrograms of LSD, our drug-subjects' AER latency slope scores changed in the direction of normal male subjects, and no significant latency slope score difference was found between our LSD-drugged subjects and normal subjects. The implications of these AER findings in relation to our other results are intriguing but since many AER scores were analyzed, the possibility must be mentioned that the AFR effect observed could have occurred by chance.

I would like to turn to a consideration of differences in the ways in which our experimental subjects reacted to LSD. The literature on the behaviors and subjective reports of LSD-drugged individuals indicates that there is considerable variability in the kinds of experiences possible. The data to be presented here suggest that individuals who differ in systematic ways in personality characteristics also differ in sensory and perceptual response characteristics and hence in the ways in which they *make sense out of* an LSD experience.

Subjective reactions of each subject were recorded by the clinical psychiatrist (D.W.) on the research team with the aid of the Subjective Drug Effects Questionnaire (SDEQ) developed by Katz, Waskow, and Olssen of NIMH. The questionnaire, which contains items dealing with (a) clarity of thinking, (b) degree of ambivalence, (c) perceptual changes, (d) degree of euphoria, and (e) degree of dysphoria, was administered at the beginning of each of the four testing sessions. During the drug days (day two and day four) the questionnaire was administered approximately 45 minutes after ingestion of the drugs. Although doubtful as to the drug they were receiving on day two, all subjects knew that they were receiving LSD on day four. Whereas no remarkable symptom differences were observed between subjects on baseline day, a rather marked range of symptom scores was recorded on the three other experimental days. On the basis of total symptom scores on LSD day *and* on the day following LSD ingestion, subjects were differentiated into two groups (Table 1). Analyses of the test battery were then carried out on the basis of this two group distinction.

**Table 1.—SYMPTOM SCORES FOR EIGHT SUBJECTS ON THE SDEQ**

| | Subject | No. symptoms LSD day | No. symptoms post-LSD day | (No. symptoms amph. day) |
|---|---|---|---|---|
| Group I | A | 95 | 46 | (63) |
| | B | 71 | 40 | (62) |
| | C | 59 | 36 | (70) |
| | D | 59 | 48 | (44) |
| Group II | E | 44 | 15 | (45) |
| | F | 40 | 2 | (38) |
| | G | 33 | 3 | (48) |
| | H | 33 | 1 | (31) |

## I. CLINICAL AND PERSONALITY TESTING

A. Clinical Psychological Testing. The clinical psychologist (W.S.) on the research team was given a list of the subjects in each group, but not one bit of information regarding their behaviors *on* or *off* drugs. He was asked to compose summary descriptions of the personalities in the two groups of subjects. The following is excerpted from the clinical psychologist's report. His formulation regarding two personality types is based primarily upon the subjects' Rorschach test verbalizations.

> There was a fundamental difference of approach to the inkblots between type I [Group I][10] and type II [Group II] subjects —a different relationship between the observer and the observed inkblots. While Group II [Low Symptom report] subjects *acted upon* the inkblots, actively analyzing, dissecting, structuring, and with a strong sense of authorship of their own percepts, Group I [High Symptom report] subjects demonstrated an attitude that the *inkblots* authored the percepts, to which they only gave voice. This difference in attitude is revealed by the way in which responses were offered. Subject MC [Group II] consistently introduced responses with such phrases as, "The very first thing I notice that it reminds me of . . ."; "I do see a . . ."; "I also see . . . ." In contrast, Subject SN [Group I] used such expressions as, "This looks like . . ."; "There are . . . ."; and "Now it's beginning to look like . . . ." Group I subjects seemed to accept uncritically the meaning presented by the inkblots, submitting to the immediate stimulus without reservation or judgment, letting

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[10] Bracketed words are my inserts.

the inkblot change its form and meaning before their eyes. There was no tension created by *no meaning,* no particular investment in finding *many meanings.* The horrifying was no more rejected than was the pleasant if it was presented by an inkblot. *Nor was any response rejected because it would fail the test of consensual reality.* In striking contrast to Group II subjects, whose responses were consistently reasonable (even at the expense of form appropriateness), Group I subjects developed responses which, while they fit the inkblots well enough, were often unreasonable or absurd. . . . Absurdity or paradox apparently created no tension for Group I subjects. They were able to admit absurd, paradoxical, or "unrealistic" ideas suggested by an immediate (inkblot) stimulus. . . . Group I subjects apparently have more basic trust in people, and when anxious about interpersonal stresses, seek to resolve them in interpersonal interaction. Group II S's, in contrast, become distrustful when anxious, and rely on their own internal resources to resolve the anxiety.

B. Clinical Psychiatric Impressions. The inferences regarding the two personality types derived from the Rorschach test were clearly similar to the impressions recorded *independently* by the clinical psychiatrist (D.W.) who had administered the SDEQ.

Group I. Open, experiencing, able to "let go" of controls and "go with the drugs." Score high in openness to contradictory experience on SDEQ.

Group II. Analytic, rational emphasis on thinking rather than feeling, less open to change. Under the effects of the drugs they report relatively little subjective change. Highly motivated to stay in control and to structure their experiences. Rarely experience contradictory feelings.

C. Personality Questionnaires—Several personality questionnaires were administered to each of the subjects on baseline day. The procedures were the Stimulus Change Seeking Scale,[20] the Pleasantness-Unpleasantness Word Use Scale,[21] the well known Maudsley Personality Inventory, two other short questionnaires of Introversion-Extroversion (IE), and the Welsh Anxiety Scale. (None of the IE measures discriminated between the two types of LSD reactors.[22])

1. Stimulus Change Seeking Scale—the higher scores of subjects in Group I as compared with those in Group II were consistent with the clinical psychological and psychiatric evaluations. Group I subjects' higher scores were indicative of a greater degree of stimulus-seeking behavior and a greater receptivity to novel stimulation during ordinary, everyday situations (Table 2).

Table 2.—STIMULUS CHANGE-SEEKING SCORES OF TWO GROUPS OF LSD REACTORS DIFFERENTIATED ON THE BASIS OF SDEQ SCORES

| Group I | | Group II | |
|---|---|---|---|
| Subject | Stim. chg. score | Subject | Stim. chg. score |
| A | 31 | E | 21 |
| B | 25 | F | 23 |
| C | 29 | G | 18 |
| D | 27 | H | 24 |

2. Pleasantness-Unpleasantness Word Use Scale—Higher scores tended to predominate in Group I. These scores were indicative of a tendency for Group I subjects to use more unpleasant words and to be more open to unpleasant ideas and affects than Group II subjects (Table 3).

Table 3.—PLEASANTNESS-UNPLEASANTNESS (PUP) WORD USE SCORES OF TWO GROUPS OF LSD REACTORS

| GROUP I | | GROUP II | |
|---|---|---|---|
| Subject | PUP score | Subject | PUP score |
| A | 12 | E | 8 |
| B | 16 | F | 14 |
| C | 16 | G | 5 |
| D | 10 | H | 9 |

3. Maudsley Personality Inventory (abbreviated version) Neuroticism Score—although a clearcut difference in Neuroticism

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[20] Garlington, W.K., and Shimota, H.E. The change seeker index: a measure of the need for variable stimulus input. *Psychological Reports,* 14:919–924, June 1964.

[21] McReynolds, P., and Ullmann, L.P. Differential recall of pleasant and unpleasant words as a function of anxiety. *Journal of Clinical Psychology,* 20:79–80, January 1964.

[22] The Meyers-Briggs indicator was not among the questionnaires used.

scores was not found between the Groups, the two highest Neuroticism scores were found in Group I and the two lowest Neuroticism scores were found in Group II. This is a curious finding in relation to the other data obtained in that the more "receptive to stimulation," more "open to unpleasant ideational stimuli" subjects (Group I) also had the high Neuroticism scores. High-scoring subjects admitted to (i.e., responded YES to) the six items which comprise the Neuroticism scale whereas low-scoring subjects responded NO to most of the same items:

1. Do you sometimes feel happy, some times depressed without any apparent reason?
3. Do you have frequent ups and downs in mood, either with or without apparent cause?
5. Are you inclined to be moody?
6. Does your mind often wander when you are trying to concentrate?
9. Are you frequently "lost in thought" even when supposed to be taking part in a conversation?
11. Are you sometimes bubbling over with energy and sometimes very sluggish? [23]

**Table 4.—MAUDSLEY PERSONALITY INVENTORY NEUROTICISM SCORES OF TWO TYPES OF LSD REACTORS**

| GROUP I | | GROUP II | |
|---|---|---|---|
| Subject | MPI score | Subject | MPI score |
| A | 0 | E | +1 |
| B | +6 | F | −2 |
| C | +6 | G | −4 |
| D | 0 | H | 0 |

Note: A Zero score indicates that a subject answered half YES, half NO. A positive score indicates that more items were answered YES; a negative score such as a —4 indicates that five items were answered NO and one item was answered YES.

## II. SENSORY-PERCEPTUAL TESTING

Taken together, the clinical and personality testing suggested a relatively clearcut basis for differentiating subjects into two categories. The next step was to develop hypotheses regarding the relationship between the personality-trait patterns of the two groups and their modes of registering and organizing sensory input. Primarily on the basis of work done by myself and my colleagues,[24-27] I formulated the following hypotheses regarding behavior under the influence of LSD:

A. Subjects in Group I will evidence lower sensory thresholds (i.e., will be more sensitive) than subjects in Group II on the audiometric threshold procedure.

B. Subjects in Group I will evidence greater impairment than subjects in Group II in their ability to organize and articulate speech stimuli into meaningful patterns on Henkin's auditory integration procedure.

C. Subjects in Group I will evidence greater responsiveness to irrelevant, contextual cues than subjects in Group II on our measures of "anchoring" of psychophysical judgments.

D. Subjects in Group I will evidence a greater tendency than subjects in Group II to reduce automatically the experienced intensity of strong stimulation. This response disposition, which usually is inferred from performances on a kinesthetic figural aftereffects test, has been studied extensively in our laboratory and in Aseneth Petrie's laboratory.

For each of the four measures, a trend was found in the predicted direction. On the whole, the trends were more clearly apparent in subjects who were lighter in weight. This latter finding was consistent with the results of a number of other investigators' findings [28] that the relationship between the microgram dosage of LSD used in the experiment and the body weight of the subject is an extremely important consideration. It is an especially important consideration in low-dosage experiments. In the present study in which a 50 microgram dosage was employed, differences between the two groups usually were apparent in subjects who weighed less than 70 kilograms. It is suggested that the lighter-weight subjects were more affected by the 50 microgram dosage and thus were more prone to evidence their unique patterns of adjusting to an LSD-induced altered state of consciousness.

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[23] The term Neuroticism is not the term of choice of this investigator for describing individuals with many Yes responses. It is considered *misleading* and is retained only because it has been used this way by the originators of the MPI questionnaire.

[24] Silverman, J. Variations in cognitive control and psychophysiological defense in the schizophrenias. *Psychosomatic Medicine,* 29:225–251, May–June 1967.

[25] Silverman, see footnote 16, page 15.

[26] Buchsbaum, see footnote 18, page 15.

[27] Silverman, J.; Buchsbaum, M.; and Henkin, R. Stimulus sensitivity and stimulus intensity control. *Journal of Perceptual and Motor Skills* (to be published).

[28] Key, B.J. Effect of Lysergic Acid Diethylamide on potentials evoked in the specific sensory pathways. *British Medical Bulletin,* 21:30–35, January 1965.

1. The lowest auditory threshold score was found in a Group I subject; the highest auditory threshold was found in a Group II subject. Recall that all LSD subjects demonstrated an unusual sensitivity on the audiometric procedure. Perhaps because the "range of talent" was so skewed in the greater-sensitivity direction, no further differentiation between the groups was possible (Table 5).

2. There was no overlap in the scores of the two groups on the auditory integration measure. Group I subjects evidenced greater impairment than Group II subjects in their ability to organize and articulate speech stimuli into meaningful patterns (Table 6).

**Table 5.—AUDITORY THRESHOLD SCORES OF SUBJECTS UNDER THE INFLUENCE OF LSD-25**

| GROUP I | | | | | GROUP II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Auditory threshold score | Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Auditory threshold score |
| A | 62.0 | 95 | 46 | −10 | E | 70.3 | 44 | 15 | −15 |
| B | 67.5 | 71 | 40 | −20 | F | 76.4 | 40 | 2 | − 5 |
| C | 99.3 | 59 | 36 | −10 | G | 55.6 | 33 | 3 | −10 |
| D | 72.0 | 59 | 48 | −15 | H | 64.5 | 33 | 1 | −10 |

Note: The higher the negative number, the greater the sensitivity of the subject, i.e., the lower the auditory threshold.

**Table 6.—AUDITORY INTEGRATION SCORES OF SUBJECTS UNDER THE INFLUENCE OF LSD-25**

| GROUP I | | | | | GROUP II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Integration score | Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Integration score |
| A | 62.0 | 95 | 46 | −18 | E | 70.3 | 44 | 15 | +4 |
| B | 67.5 | 71 | 40 | −12 | F | 76.4 | 40 | 2 | −4 |
| C | 99.3 | 59 | 36 | − 8 | G | 55.6 | 33 | 3 | +4 |
| D | 72.0 | 59 | 48 | −12 | H | 64.5 | 33 | 1 | 0 |

Note: The larger the negative number, the greater the impairment in auditory integration.

3. The highest "anchoring" scores, indicative of hyper-responsiveness to irrelevant stimuli during perceptual judgment tests, were found in Group I; the lowest "anchoring" scores were found in Group II (Table 7).

**Table 7.—ANCHORING SCORES OF SUBJECTS UNDER THE INFLUENCE OF LSD-25**

| GROUP I | | | | | GROUP II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Anchoring score | Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Anchoring score |
| A | 62.0 | 95 | 46 | 15 | E | 70.3 | 44 | 15 | 2 |
| B | 67.5 | 71 | 40 | 14 | F | 76.4 | 40 | 2 | 7 |
| C | 99.3 | 59 | 36 | 6 | G | 55.6 | 33 | 3 | 12 |
| D | 72.0 | 59 | 48 | 5 | H | 64.5 | 33 | 1 | 11 |

4. Perceptual performance scores indicative of a *reduction* in the experienced intensity of strong stimulation were clear-cut in three out of four Group I subjects. Not one subject in Group II evidenced behavior on the figural after-effects procedure which was indicative of pronounced sensory input *reduction* (Table 8).

Table 8.—STIMULUS-INTENSITY REDUCTION SCORES OF SUBJECTS UNDER THE INFLUENCE OF LSD-25

| | | GROUP I | | | | | GROUP II | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Reduction scores | Subject | Body wt. in kg. | # Symptoms LSD day | Post LSD day | Reduction scores |
| A | 62.0 | 95 | 46 | −2.0 | E | 70.3 | 44 | 15 | +0.8 |
| B | 67.5 | 71 | 40 | −2.0 | F | 76.4 | 40 | 2 | −1.3 |
| C | 99.3 | 59 | 36 | −2.3 | G | 55.6 | 33 | 3 | −1.3 |
| D | 72.0 | 59 | 48 | −0.3 | H | 64.5 | 33 | 1 | −0.8 |

Note: Scores of —2.0 or greater are indicative of significant stimulus-intensity reduction responsiveness. Smaller number negative scores are indicative of less pronounced reduction responsiveness.

In summary, the results of this pilot study are not inconsistent with the hypothesized relationships, especially among lighter-weight subjects. On the basis of clinical and personality testing, it appears that Group I subjects are more open, receptive, and seeking of environmental and internal stimulation than Group II subjects. On the basis of the LSD-day sensory-perceptual testing, Group I subjects are found to be quite sensitive to low-intensity auditory stimulation and tend to reduce the experienced intensity of strong stimulation to a greater extent than Group II subjects. Group I subjects also evidence more impairment on tests of perceptual integration and judgment. The greater impairment in perceptual functioning which is characteristic of Group I subjects under the influence of LSD is consistent with their disposition to yield to the drug experience, to "go along with it," rather than to counteract its effects. Since LSD induces a state in which attention to everyday events (e.g., sensations, ideas, memories) is dramatically altered, it is not surprising that ordinary perceptual functioning is impaired and that it is more impaired in open, receptive individuals. The unusual reaction to LSD–25 is typically one in which *no* impressive impairment in perceptual and cognitive functioning occurs. Indeed, a concerted attempt on the part of an individual to maintain an active analytic intellectual style rather than to yield psychologically (and physiologically) to the effects of LSD, is probably an important precursor of an aborted LSD experience.

Until further research has been carried out, all of the above inferences must be considered as, at the most, tentative ones. The very small number of subjects in the sample, the lack of clear-cut differences, in some instances, and the small dosages of LSD–25 employed are just a few of the factors which limit the kinds of conclusions which can be drawn from this study. I believe, however, and with good reason, that future investigations in this field will confirm and expand upon our work and that the kind of research strategy described here will contribute in a significant way to our understanding of human behavior.

**Dr. Meyer:** Now we turn to Dr. Frosch.

**Dr. William Frosch:** I would like to start by referring to the problem that Dr. Shagass brought up concerning recurrent experiences. These first came to my attention when our research group received a call from the admitting office saying, "We have a crazy guy down here who sounds like he's on a trip, but denies it. Do you want to see him?" We did. The patient came up and said, "Doctor, there is something wrong with me; my wife says I'm beginning to talk crazy. I've never talked this way before and things are beginning to look funny, just as they did when I took LSD." He attributed the changes in perception and in self-feeling to his earlier LSD experience. He was terribly worried that he had perhaps permanently damaged himself and this was why he had come to the hospital. He insisted that these kinds of experiences had never occurred to him before. He was a good historian and in many ways one of the most stable of the people we had seen. He had a wife and children and worked as a junior executive and has continued to do so. While it is difficult to evaluate such post-hoc reports, it is likely that he had not been psychotic or pre-psychotic prior to his earlier LSD trip. The drug may have changed or triggered something. The presenting symptoms were not only transient anxiety states, but were also very characteristic perceptual distortions of the sort that are usually associated with LSD (e.g.: kaleidoscopic color changes). These recurrent states were, however, associated with events in his mental life. For example, this man had a difficult situation with his boss, and as he looked at his boss' face it would begin to break up into kaleidoscopic patterns. He lost his job as a result of this situation. In summary, while some of our patients very clearly link the onset of these recurrent experiences to their ingestion of LSD, the episodes are frequently triggered by real events and may represent phenomena or exaggerations of phenomena perhaps previously experienced (i.e.: prior to LSD ingestion).

In viewing adverse reactions generally, we have had an average of two patients a week admitted to Bellevue for whom we feel that the LSD experience played, at the very least, a precipitating role in the admission. As was said in the circulated paper, we've seen many, many more people who had LSD experiences, but who were hospitalized for some other reason. These were usually acute schizophrenic episodes which, as far as we can determine, were unrelated to the previous drug experience. Whether this average admission rate (two patients a week) really represented a stable admission rate is difficult to determine. Initially we saw almost all of the patients with this problem in the New York City area. In the intervening year or so, some other hospitals have begun to admit them. Dr. Hirschhorn tells me that Mount Sinai has now been seeing a number of these patients, and I know that in the last year Kings County has evaluated and admitted many patients with this diagnosis. This may represent an increasing admission rate.

Although my research group hasn't seen all of the LSD patients, we have studied a number of samples over the years. Each sample is essentially identical to every other in terms of the basic demographic characteristics, as well as the clinical picture. In contrast with the usual Bellevue population, they are all young, middle class, and almost exclusively white. This is certainly consistent with our usual stereotype of this population. It is of interest, however, that the Kings County sample has a relatively high proportion of Negroes and is a lower class population. Kings County also feels that their patients' involvement with LSD starts with the onset of a psychosis. They seek out the drug in an attempt at self cure. This has certainly been true for some of our patients, but doesn't seem to have been true for all.

We've done routine psychological testing on some of the patients that we've seen. Once the acute episode is over, we've been unable to determine anything that would be described classically as organicity on either the Wechsler scales or the Bender-Gastalt. We've also done EEG's. Within the three days following admission we've seen some non-specific "drug-effect EEG changes." These are transient and may be related to the ingestion of other drugs in the period preceding admission. In fact 90 percent of the patients admitted because of LSD have had experience with amphetamines; two-thirds have taken barbiturates; and, rather surprisingly, about one-half have tried one of the opiates. As one would expect, there is an almost universal use of marihuana in this group. We've seen only one patient who had never used marihuana. This woman was somewhat unusual in other respects. She was a woman of 34 who went to a psychologist looking for help. She claims that the psychologist said, "Here is some LSD, go home and take it." She had an acute psychotic reaction. She is now furious and has an evangelical anti-LSD attitude.

Several years ago Dr. Korein and Dr. Musacchio from our department were interested in the use of LSD to unmask latent neurological defects, similar to the way amobarbital may induce focal weakness. Since many of the effects of LSD are sensory, they felt that administration of LSD might induce sensory disturbances in patients with neurological disease. They administered 100 micrograms of LSD intravenously to 14 patients with sensory disorders resulting from focal cerebral diseases. These included visual field defects and hemisensory defects.

All of the patients had symptoms within five to ten minutes. The usual initial symptom was drowsiness which, as in Hoffman's original description, was described as a feeling of dizziness and drunkenness. Nine of the 14 patients showed anxiety and agitation, three had alternating euphoria and depression. Six had what the investigators (who were neurologists) termed clinical psychosis—consisting of hallucinations, depersonalization, and marked anxiety. In three subjects the reaction was "violent" and in two the procedure was interrupted with chlorpromazine. There were specific neurological effects in all of the 12 patients on whom data could be obtained. In three out of four patients a mild aphasia became worse. There didn't seem to be any change in the organic mental syndromes which were mildly present in four patients. Five of the seven patients with homonymous visual field defects showed visual changes such as flashing lights, or distortions of color or distance. There were lateralized somatosensory distortions which appeared to be related to the locus of the cerebral disease in patients with hemisensory defects. One patient had a localized clonic seizure of the upper extremity. The EEG appeared "less abnormal" after administration of LSD. There was a decrease in the amount and/or amplitude of slow-wave activity.

I would also like to comment on Dr. Silverman's suggestion that hypersensitivity is an impairment of sensory integration. Clinically, in those patients whom I have been able to observe during a recurrence, this seems to be what's going on. While sitting with me, a patient will hear a sound. This distracts him and he will get lost in a perceptual distortion.

One final word, we've seen very little DMT (Dimethyltryptamine) or DET (Diethyltryptamine) resulting in hospitalization even though it apparently is present in New York. I wonder if this is related to the length of the trip. Even a "bad" trip doesn't last long enough for them to get to the hospital. We've also had one drug sample which was reputed to be STP. It was a green-blue-grey tablet. One-half of this tablet, which weighed 172 milligrams, was given intravenously to a dog. Nothing was observed except mild fore-limb tremor which may have been related to the fact that it was a suspension rather than a solution that was injected. Chemical tests have not yet been completed.

COMMENT FROM AUDIENCE: Most of these mescaline-type compounds are extremely difficult to get any kind of evidence and analysis on.

**Dr. Frosch:** Some of the original descriptions of STP sounded to us like a Ditran effect, but it's very clearly not a Ditran-related compound. The only thing I know of that would distinguish a mescaline-like drug from a Ditran-like compound is whether the patient has a mydriasis with or without cycloplegia. Dr. Samuel Gershon who ran the dogs is very "hep" on anticholinergics. I would accept his findings that it is not a Ditran-like compound. I think that he would know.

**Dr. Meyer:** Thank you very much. I would like to go on to Dr. Smith who will talk about the West Coast scene.

**Dr. David Smith:** A number of questions have been raised relative to drug practices in the Haight-Ashbury district of San Francisco, and I'll look forward to discussing these questions during the question and answer period. In this part of my presentation, I'd like to focus primarily on our specific experience with the compound STP. As I'm sure you know, STP is in effect a "proprietary name" established by the underground or black market. It means serenity, tranquility, and peace. The generic name for this chemical substance is DOM or 2,5–dimethoxy–$-\alpha$, 4-dimethyl phenethylamine. It is a compound related to the amphetamines, but it has some very unusual and different properties which were very surprising to us. In this presentation I'll attempt to describe not only the clinical properties of the drug, but also its introduction into a highly susceptible drug-using population.

First I would like to describe the population into which STP was introduced. We first heard reports of STP by "psychedelic leaders" as early as February 1967, but the first written reports appeared in the underground newspapers—following a predictable marketing pattern. The *Berkeley Barb* described the compound as being a guaranteed "good" trip that was not yet illegal. We heard enough of these reports to know that something was coming.

On June 6, 1967, we opened the Haight-Ashbury Medical Clinic which was a general medical facility dealing with the hippies in the Haight-Ashbury. The population at risk during the summer was by no means homogeneous. We have a large drug survey going now, entitled "Drug Practices in the Haight-Ashbury Subculture." Our data have not been completely analyzed but our impressions to date are that the population at risk was composed essentially of three major groups. First of all, there was a large group of teenagers who were in Haight-Ashbury primarily for the summer experience. They had not, by and large, had experience with any drug but marihuana, although some may have taken LSD one or two times. In essence this group was oriented toward taking drugs, but had very little experience. The second group consisted of individuals who had built their philosophy around the mystical and evangelical experiences of LSD. They are of the "drop-out category," and were fully committed to the hippie philosophy. Many were actively involved in some of the local organizations in the Haight-Ashbury, such as The Diggers, The Straight Theatre (a community cultural center), our clinic, etc. The third group can be described best as an odd mixture of sociopathic personalities (including the motorcycle gangs) that came to Haight-Ashbury for a variety of reasons. Certainly amongst this group there were a lot of compulsive drug users. Some of these individuals had a long previous history of multiple drug abuse patterns.

Although we heard reports of the STP being used, we did not see a case in the San Francisco area until June 8, and this seemed an isolated event. However, on June 21 at a hippie celebration of the summer solstice (one of a series of events held in the Haight-Ashbury "summer of love festival"), 5000 STP tablets were given away without charge in the panhandle of Golden Gate Park. Very soon after that we saw a number of adverse reactions to STP. The tablets that were distributed on this occasion were all stamped out of the same die. We have reports that approximately 15,000 of these aquamarine tablets were distributed and that many have since been turned over to the Food and Drug Administration for chemical analysis. We have evidence that no new STP tablets have been introduced into the Haight-Ashbury since that time except for some amphetamine labelled as STP (in order to get a higher price for that material).

I think it would be advisable for me to describe the clinical STP syndrome to give you some idea of how our clinic handled the situation of an unknown drug. We have a population of 10,000 to 20,000 people in the Haight-Ashbury, but this is a very transient population. LSD use approaches 90 percent. At least 50 percent of the population had been there less than two months and had come primarily for the summer. We estimate that during the summer of 1967 there were at least 100,000 persons passing through the community, although the steady state population would be between 10,000 and 20,000. Our Haight-Ashbury Clinic saw 10,000 medical cases in three months.

Now, the clinical STP syndrome, as we initially saw it, was of long duration and it was this long duration that produced many of the "bad" trips. Many of the patients said that they experienced initially good feelings, but that the long duration of the STP trip (72 hours) produced a fear and panic with concerns that they would "not come down." There were marked and vividly colored hallucinations. Many of the individuals who had taken LSD more than 100 times, and were therefore very experienced with psychedelics, described themselves as encountering their first "bad" trip with STP. They described the experience as being more intense, and lasting so long that eventually an adverse reaction developed.

We saw almost universally a very rapid tachycardia with fine muscle tremors, and dilated pupils that were sluggishly reactive to light and accommodation. I think that at the time we should have been in a better position to describe this as not being an atropine-like compound. However, we had heard of the possibility of the Ditran series being introduced into the community and we were very much concerned because of the high incidence of delirium with these drugs. Just prior to this, we had heard that an agent which had been used for Army chemical warfare had been stolen, and these vague rumors and the physical syndrome that we were seeing made us think initially that we were dealing with an atropine-like substance. At the end of June we saw 20 cases enter the clinic; we had no idea what the compound was which had been ingested.

In the city of San Francisco thousands of adverse reactions to LSD occur. The standard approach in institutions is the utilization of large dosages of intramuscular chlorpromazine. The first few cases that were treated at San Francisco General Hospital became markedly more agitated and very disturbed after the administration of chlorpromazine. At this time our feeling was that the clinical syndrome represented that of an atropine-like drug. This seemed to explain several aggravated clinical states in which chlorpromazine was given and the patient then appeared to get worse. We were particularly disturbed because chlorpromazine is a very important drug on the Haight-Ashbury black market and we knew that for every one case that was seen in institutions at that time prior to the opening of the Haight-Ashbury Medical Clinic, at least a hundred cases were treated outside of institutions with self medication. We therefore published widely in the underground literature that chlorpromazine was contraindicated, and that those having STP reactions should come to the clinic where there would be medical assistance without legal repercussions.

In July, chemical analysis revealed that this compound was a substituted phenylethylamine and that this was not an anticholinergic compound. However, in reviewing our hospital data it would appear from our results that the question of chlorpromazine is still unsettled. Our initial results and impressions with cases that have occurred since that time indicate that this phenothiazine in no case interrupted or shortened the duration of the hallucinatory experience. There is at the present time (September 1967) very little STP usage. The majority of the approximately 50 cases that we studied in detail came in the months of June and July. The drug rapidly lost favor for a variety of reasons, but I think that we can now come up with some valuable recommendations as to a treatment regime. In a forthcoming paper which Dr. Fred Meyers and I will publish, we divide the STP cases into the following four major categories:

1. "Good" trips occurred in a significant number of people who took STP and who were able to handle the experience. These people were predominantly those who had had a lot of experience with LSD, and a very low liability to adverse reactions. They considered the STP experience to be the "caviar of the psychedelic experiences." This group still takes STP periodically.

2. Some "bad" trips were handled by the community.

3. Some "bad" trips were handled by the Haight-Ashbury Medical Clinic which deemphasizes chlorpromazine treatment and emphasizes the use of a non-professional guide to sit with the individual and try to talk him through his experience. We have found that (as in the LSD experience) the patient can be seen by a physician and encouraged to work with either a physician or a sympathetic individual to alleviate an acute panic reaction (the major and dominant reaction seen in the Haight-Ashbury).

4. Some "bad" trips were admitted to the hospital. At our county hospital the supportive psychotherapeutic approach is deemphasized because of lack of personnel, but the regime of chlordiazepoxide as a sedative and chloral hydrate as a hypnotic seemed to have good results in calming much of the anxiety and seemed preferable to chlorpromazine.

The hospitalized patients had a much higher incidence of long-term psychological problems (depression, "flash-backs," etc.). One sample case illustrates some of the reasons for this. An individual had taken an unknown drug and was admitted to the hospital actively hallucinating. The psychiatrist on the ward gave him a large dose of chlorpromazine and when the hallucinations did not clear, gave him progressively increasing doses of this drug to 800 mg. four times a day. The reaction became progressively worse and on the tenth day the individual walked out of the hospital never to be seen again.

To summarize, in areas where there is a high incidence of psychedelic drug-usage there is far too much dependence upon the phenothiazines. We would recommend that when in doubt, the phenothiazines should not be used, that these very extreme hallucinatory experiences can be handled with sedatives and supportive psychotherapy.

In conclusion, I would like to state that it is very disturbing to us that the gap between the psychedelic drug-using population and the scientific and medical community is widening so rapidly. We are now faced with the introduction of another hallucinogen in the DOM series. This drug is called MDA. MDA is the chemical name; the proprietary name for this compound was to be FDA but the underground black market decided to change their approach, probably because the STP got a lot of bad publicity which essentially killed the market. When the scientific community is not in contact with the drug-using population, then the scientific community is hit with a series of surprise "shock waves." In particular, those of us who are on the psychedelic front lines are faced with a mass of patients who have ingested the unknown compound and are having a reaction that is very difficult to define.

I would like to close by asking that the scientific community make more of an attempt to come into contact with the drug-using population. One of the major problems with the population in the Haight-Ashbury is that they have essentially turned away from institutions and will not seek traditional medical help. They are left to their own devices, which tend to potentiate and propagate the patterns of drug abuse.

We must realize that a majority of the "adverse reactions to hallucinogenic drugs" (which is the title for this symposium) are happening outside of our institutions. If our studies do not emphasize more research of the participant-observation type then our information about this topic will continue in its present state of inadequacy.

**Dr. Freedman:** I do want to say one thing about chlorpromazine. At Yale we stopped giving it for bad reactions several years ago. We gave amytal just as we would in a seizure state if we had to. Generally we gave supportive therapy. As a result, we never had any contaminating psychological reactions, that is, the chlorpromazine confusion and the LSD state. In animals it has been shown that you could stop an LSD reaction in the rat with as little as 30 gamma per kilo of chlorpromazine where the normal dose is 2 mg. per kilo. If you went higher, you got a compounded reaction, a chlorpromazine reaction and an LSD reaction. While you never know what inferences you can make from animals to man, this tipped us off as to why we were getting some confusing reactions.

The second pharmacological point that I think should be noted here is that the plasma level of LSD correlates beautifully with the period of acute effects of LSD in animals and in man. The waves of reaction that we sometimes get at least from animal data seem to be due to the fact that LSD is sometimes held in tissues and then comes out suddenly into the plasma several hours later.

QUESTION: What tissues?

**Dr. Freedman:** We don't know yet. As I've said, we have monitored plasma concentrations. I have wondered whether STP and its duration of actions shouldn't be monitored as you would any other pharmacological problem—that is, let's get plasma levels and see what's happening.

Can I also just raise one question? What is the actual length of duration of the STP reaction?

**Dr. Smith:** It was between 16 and 72 hours. We had one case of an undiagnosed, prolonged acute brain syndrome that lasted for 10 days in which the individual was actively hallucinating and out of contact with reality. In this particular situation the patient had been exposed to progressively and increasingly higher doses of phenothiazine in addition to his previously ingested STP.

The first group who came into our clinic complaining of adverse reactions stated that they were on a "death" trip. The rapid tachycardia induced by the STP led to the fear of a heart attack. Thus, aspects of "What will happen when I die?" were introduced into their minds, followed by a panic reaction. In our "calm center" we have attempted to treat these problems merely by sitting and talking with the patient; explaining that all he was having was a rapid heart rate which would go away. In other words, by explaining the symptom we have endeavored to divert his mind from thoughts of death. Many times this has been all that was necessary to stop a "bad" trip. On the other hand, these same individuals when allowed to progress on the street might end up at the San Francisco General Hospital, running down the street away from something in a very acutely paranoid state. The point is that if you can reach these patients at a very early stage in their psychotic reactions, many times you can interrupt it. However, if the individual is forced to go through waiting lines, ambulances, police, etc., this merely aggravates the reaction. I think this is the reason that the cases at the county hospital were so severe and extreme and sometimes related to self-inflicted wounds.

**Dr. Meyer:** Dr. Frosch, Dr. Ditman, and Dr. Ungerleider—is it your experience as well that phenothiazines perhaps are contraindicated in the management of some of the acute adverse reactions?

**Dr. Ditman:** I would say no.

**Dr. Ungerleider:** Let me say that we have seen six or seven paradoxical reactions to chlorpromazine when we gave up to 3,000 mg. per day. One case was described in which the patient showed neither improvement nor exaggeration of symptoms until we stopped the chlorpromazine after which the patient improved. These paradoxical reactions to chlorpromazine have been reported, however, not only in the treatment of adverse LSD reactions but in the treatment of schizophrenia as well.

**Dr. Frosch:** We have been impressed with the fact that many of our patients don't respond to phenothiazines. I am not so sure about the paradoxical reactions. There may be a few but many of them go right on their merry way. Additionally, we have hesitated to add something when we knew so little about what was going on to begin with. It sounds as though many of the management problems are best handled by reassurance and by discreet use of hypnotics.

**Dr. Freedman:** May I raise one point. Back in 1956 Mayer-Gross[29] described chlorpromazine as a psychotomimetic. This statement actually appears in one of his papers. He found that when it was given to normal people they had peculiarly colored dreams and in one or two very well recorded cases people had psychotic-like responses to it.

I also think it is important that we know what we are treating. We are treating panic, depression, and hallucinations; we are not just treating a kid because he has dropped out of law school.

**Dr. Meyer:** At this point, I would like to cut off discussion until we hear from Drs. Ditman and Osmond whose presentations will round out the morning session.

**Dr. Keith Ditman:** What I am going to talk about today is a study in which we tried to determine the harmful aspects of the LSD experience.

My experience with LSD goes back over the past 11 years, during which time I have been interested in LSD as a possible psychotherapeutic adjunct, particularly with alcoholics. I have also been interested in developing instruments that could give us a better understanding of the nature of the LSD experience. To this end, John Whittlesey, Thelma Moss, and I have developed a card sort which is an instrument to obtain a retrospective description of a person's LSD experience. It can be used actually for any consciousness-changing experience, but is particularly useful for the LSD experience.

In following the current revival of the use of hallucinogens and studying the literature of antiquity, I am impressed with the lack of reported psychiatric complications among the Indians and others who have used various hallucinogenic drugs. This apparent safety led many research investigators to view these compounds benignly (until recently). We should have been more aware of the abuse potential of these substances. Some 70 years ago Havelock Ellis published on mescaline in *Lancet*,[30] predicting that it had a real future as an abuse substance. In my early experience with LSD I saw some abuse, even among professionals. I think it was here (among the professionals) that the abuse started. I suppose that we could have anticipated the abuse of LSD, but perhaps not to the extent that it has gone. In 1961, I first became aware of a person selling sugar cubes with illicitly-made LSD in them. Dr. Sidney Cohen and I began reporting on this at that time. This was the beginning of the black marketing of illicitly-made LSD. One of the earliest casualties of illicit LSD that I know of was a 14-year-old boy. He had the recurrent symptoms that Dr. Frosch has mentioned. The symptoms went on for a period of a month or more.

I would like to digress slightly here. It is not only with LSD that you see such "flashbacks." They are reported for $CO_2$ therapy and we are all familiar with the alcoholics' account of the "dry drunk." I suspect that suggestion is an important factor in this syndrome.

With our card sort we have been trying to study the nature of the LSD experience; to compare experiences for those who need treatment afterwards with those who need no treatment, or even claim beneficial effects from the experience. We obtained card sorts on 116 subjects whom we divided into three groups: those who apparently needed no treatment or even claimed benefit, those who needed out-patient treatment, and those who needed hospitalization. Group I, the largest in number, consisted of 52 persons, none of whom needed psychiatric care because of the LSD experience. This group is of considerable interest because a great majority of subjects were functioning either at jobs or as students at the time of testing. Many reported having had several drug experiences. This population was recruited through a variety of community contacts, including students, patients, and colleagues. I cannot state that they are really comparable to the other two groups, other than that they claimed that they had taken LSD. Group II is composed of 27 subjects who applied either privately or through clinics for psychiatric out-patient care, apparently as a result of their LSD experiences. As with Group I, a majority of these subjects were employed at the time of testing and reported multiple-drug experiences. Group III is composed of 37 subjects seen in psychiatric hospitals in the Los Angeles area where they had been hospitalized as a result of their LSD sessions. Again a multiple-drug experience was reported for Group III, but unlike Groups I and II, many of these subjects were unemployed.

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[29] Ginzel, K.H., and Mayer-Gross, W. Prevention of psychological effects d-Lysergic Acid Diethylamide (LSD-25) by its 2-Brom derivative (BOL 148). *Nature*, 178:210+, 1956.

[30] Ellis, H. A note on the phenomena of mescal intoxication. *Lancet*, 1540–1542, 1897.

The card sort we used in this study has 156 items descriptive of the LSD experience. The subjects were asked to sort the items into five piles, depending on how descriptive of their experiences they were. The headings of these five piles were:

1. Very much like the experience
2. Like the experience
3. Neither like nor unlike the experience
4. Unlike the experience
5. Very unlike the experience

We have classified, according to our own impressions, the items in this card sort into the following 12 categories:

1. Strong Pleasant Emotions
2. Self-Understanding and Aesthetic Appreciation
3. Mystical and Paranormal Sensations
4. Empathy
5. Religious Feelings
6. Unusual Though Not Unpleasant Body Sensations and Perceptions
7. Somatic Discomfort
8. Depression
9. Paranoia
10. Anxiety
11. Hallucinations
12. An Evaluation of the Experience

Surprisingly, the frequency of LSD usage shows no significant differences among the three groups. The percentage of Group I subjects (the ones who did not need treatment) reporting 25 or more sessions with LSD, was 35 percent as compared with 38 percent in Group III (the hospitalized group). The percentage of subjects who reported taking LSD only once was relatively small in all groups; 25 percent in Group I to 11 percent in Group III. Similarly, histories of other drugs taken by these 116 subjects revealed almost parallel percentages in all three groups; 53 percent in Group I, 67 percent in Group II, and 63 percent in Group III. In other words, over half of these people reported casual to frequent usage of various drugs, stimulants, sedatives, tranquilizers, and hallucinogens. I suppose that we were sampling the drug culture. The only group reporting use of hard narcotics, however, was Group III, with 23 percent in that category so reporting. We feel that personality factors have contributed to the hospitalization of Group III. The percentage of persons functioning at work or as students decreases from 88 percent in the non-treatment group down to 39 percent in the hospitalized group. A Chi Square test of this data reveals significance at the .001 level. It should be noted that the level of functioning was assessed just prior to interviewing and not before the LSD experience.

I do not have time to go over the 41 items which differentiated among the three drug groups, other than to say that those who needed treatment had experiences indicating marked anxiety, depression, feelings of persecutory paranoia, and fears of going insane. Such emotions and thoughts were far more prevalent in the treatment groups than in the non-treatment groups. This was at .01 level of confidence or better for all 41 items. The one item which differentiated among the three groups more than any other item was, "I felt that I might become permanently insane." Curiously, the hospitalized group (as compared to the out-patient group) did describe some aspects of their experiences as euphoric. From this data we are under the impression that it may be the nature of the LSD experiences that is causing the untoward after-effects in these individuals. In other words, LSD is *psychologically* toxic, if I may use that term. Complaints of these people after an upsetting LSD experience include anxiety, depression, borderline psychosis, psychosis, etc. I have the impression from my experience treating a number of these cases that one is dealing more with young individuals who are non-achievers, perhaps schizoid characters or borderline psychotics, and that superimposed on these problems there is the traumatic drug experience. I think that a traumatic neurosis may have developed on top of already disturbed personality or thought disorders.

**Dr. Humphrey Osmond:** During the past 15 years I have made a number of studies in a variety of contexts, using LSD–25 and other substances. Some of these studies were aimed at producing psychotic-like effects; others at treating alcoholism and other conditions; still others at studying more general psycho-social effects.

Our original subjects were university students. It was clear that they were far less able to "handle" LSD–25 than our alcoholic patients who seemed very tolerant of it and could take four to five times as much as the students.

In those early years of the 1950's one of the bitter and recurring arguments concerned whether or not the LSD experience resembled a psychosis, particularly schizophrenia. This question has not yet been completely resolved. It all depends on how you define a schizophrenic-like state and, of course, on whether you have some ways of measuring it, once it is defined. I do not believe that we could measure it at that time. We began by using the Rorschach, but many of our subjects could only do one card and that, it appears, is not enough. We tried other tests which did not work and then, early in 1960, we developed the HOD test, named in jest the Hoffer-Osmond Diagnostic test. This test was constructed following a squabble with our psychologist friends in which we rashly cast doubts upon the tests which they had been using, and they suggested rather tartly that if we were so smart we could make one ourselves. We were trapped into the attempt.

The test is extremely simple; indeed, with our lack of knowledge of test making, it could hardly be otherwise. It consists of 145 statements on cards which the test-taker sorts as true or false. Many of these statements are taken from the records or from talks with schizophrenic persons. When used by those who have taken LSD–25, we have found it best for them to take the test retrospectively, for if the test cards are given during the experience, many such subjects become extremely paranoid and one actually became catatonic. Luckily, schizophrenics are much more obliging. Even "back-ward burnt-out" cases will cooperate splendidly. They seem to be burning fiercely rather than to be burnt out. Schizophrenics on the whole take the test with zeal and alacrity. They have a test-retest correlation of about 0.9 and seem to enjoy the test and speak about it as being helpful to them. Severely catatonic patients who did not express satisfaction at the time, emphasized once they were better that it was helpful for them to know that someone had some notion of their strange predicament.

By early 1961 we had a good deal of evidence that schizophrenia and the states following the taking of LSD–25 have many similarities, in so far as our crude test showed. We knew that something more refined was needed. We had found in the HOD test that sensory perception, time perception, self perception, and perception of others were very useful. In our new instrument, the EWI (Experiential World Inventory) we had greatly increased the number of items dealing with these last three categories. Our new test shows that the characteristic which most clearly differentiates the state induced by LSD–25 from clinical schizophrenia is our Dysphoria scale.

Schizophrenics, as we have shown, are usually as, or even more, depressed than those diagnosed as having depressive illnesses, or melancholia. LSD–25 takers, on the other hand, are usually much more cheerful. Otherwise the experiences of LSD–25 takers resemble those of severe schizophrenics rather closely. It would be difficult to believe that many people would ever take LSD–25 more than once if it were always or often accompanied by severe depression and despair. The schizophrenic patient has good cause to be gloomy because he is trapped in his illness and cannot get out. The LSD–25 taker, whether his experience is pleasant or not, is always buoyed up with the thought that it will soon be over. Even when he doesn't enjoy himself much, the thought of its ending and his being able to talk to friends about his experience is a source of hope and comfort. If you cover up the Dysphoria scale, it is not easy to distinguish schizophrenia from the LSD–25 state.

There is one other significant difference: we have a scale, the impulse control scale, from which it is clear that many schizophrenic patients feel that the situation is getting out of hand and beyond their control. Most LSD–25 takers feel more or less in control, though not all are completely sure. We have found that both the HOD and EWI tests can be very useful if patients are asked to do the tests as they are now, as they were at their worst, and as they were at their best. This saves a great deal of time and allows one to estimate whether the patient is getting better or worse.

By doing our tests over a number of years, we have been able to show that most patients have a clear and rather accurate recollection of their illnesses. This is of great value clinically because one of the most difficult decisions facing the clinician is that of differentiating someone who is becoming worse from someone who is getting better.

The success of the HOD and EWI tests seems to be due in part to the fact that patients consider the statements on the cards relevant to their illness and so are very cooperative. Recently we have given our tests to people who have been frequent users of LSD–25, or at least substances labelled as such. We now have records from eight of these frequent users. Most of them are functioning well according to their standards. Their ages range from 18 to 42. They are not like schizophrenics even though they do have sensory, time, body, and self-perception disturbances resembling those found in some schizophrenics. They are overly alert, their perceptual constancy is impaired, their experience of time is peculiar, their level of consciousness fluctuates, and they have some disturbances in their body image. One might expect that such changes would impair conceptual thinking and indeed, they do complain of some reduction of intellectual efficiency, though they feel more creative. Depression is almost always low and even if they feel mildly depressed and irritable, they claim there is an underlying euphoria and that they are intrigued and excited. Paranoid features are conspicuously lacking.

Just before I left Princeton, my colleague, Dr. Moneim El-Meligi, checked on a special scale that we have been developing which we call hyperaesthesia. Seven out of eight of these LSD–25 takers scored very high on this scale, higher than nearly all normals we have studied. Something has clearly happened to them. However, it is only a small group and it is too early to draw any far reaching conclusions. These users themselves believe that they have had a change of personality which they feel is for the better. I am not quite so convinced of this, but I am certain that something has happened.

Yesterday we had a bonafide schizophrenic with whom a number of colleagues and I have been working for a year; from our clinical findings, her reports, and our tests we felt we had largely succeeded in getting her better. Ten days ago, with an appalling vexatiousness, she obtained some LSD–25, so-called, and took it. She became very much frightened after taking it on her own and went back to her earlier schizophrenic condition. Our most recent record suggests that she is now almost completely well again, after five days of schizophrenia. Our records show that her condition was not similar to that of the frequent LSD–25 users but closely resembled schizophrenia as seen in her own earlier records and that of others. She bemoaned her bad luck, to which I replied, "Sorry, bad judgment is a more appropriate label."

I was delighted to find that using different methods from ours, Dr. Silverman has come to very similar conclusions. What happens to these adventurers resembles some aspects of schizophrenia but is not identical to it. I believe that one can produce a negative LSD–25 experience that would closely resemble schizophrenia. One of the easier ways is to tell a person who is in the middle of an LSD–25 experience that he was given a placebo; this is likely to be very disturbing, but could easily be harmful and, therefore, should not be tried. If one adds a good deal of dysphoria to the LSD–25 takers' EWI records, they look very much like those of schizophrenia. Using our HOD test we have given a random mixture of the records of schizophrenics and LSD–25 takers to groups of psychiatrists, asking them to say which were which. They did not succeed, except for one group who did very well indeed. At the time, we and they did not know why they succeeded, but it seems possible that they had recognized dysphoria as being the key and so were able to do much better than we ourselves and others.

We are still not at all sure that all psychedelic substances produce the same experiences. One would expect not, as people use rather different words for describing the effects of different psychedelics. However, now that we have reliable ways of establishing a baseline for a person's experience we should be in a much better position to explore these matters in depth. Using the Experiential World Inventory, Dr. Bernard Aaronson has shown that focal disturbances of temporal and spatial perception which he produces by post-hypnotic suggestion aimed at a single perceptual modality tend to spread to other aspects of perception. This is both elegant and puzzling. We do not yet fully understand exactly what this means.

One implication of Dr. Aaronson's work which I think we should consider very seriously is that before long someone is going to find a way of producing psychedelic phenomena by post-hypnotic suggestion. I wonder what our position will be when this happens. I can find good reason now for encouraging people to keep their distance from unauthorized psychedelics, noting the low expertise of many of the enthusiastic amateur chemists involved in this work. This approach seems to be fairly effective and at least some young people heed the warning. It is a soft-sell approach; young folk who would not hesitate about vexing their elders do hesitate about becoming the victim of someone else's inept chemistry. I do not know that this technique would work in all cultures, but in the "brand name" culture of the United States, people seem willing to respond to it. It may not prevent all of them from continuing to take LSD, but it may get some of them to hesitate and even to stop. It also encourages them to use natural products which usually have a lesser degree of danger, for nature is a better chemist than many amateurs. We are encouraging psychedelic users, if they are going to undertake these hazards, at least to screen out those potential users who are obviously perceptually unstable. The HOD test allows them to do this. At least some young people are taking careful notice of this.

We have also suggested something rather more controversial, namely that those who intend to take psychedelics should have large doses of nicotinic and ascorbic acid available, for these reduce the impact of LSD–25. This has been shown to be the case in animals and in humans, though I should like to see more extensive studies done in these matters. The effect of the vitamins seems to depend upon how much is taken and to some extent upon how early in the experience it is injected. I believe that it is good for people to have something to take that does good and will not do harm; this reduces the chances of panic. Further careful studies will be needed to show how much of this beneficial effect, if any, is a placebo effect. If amateur experimenters can be persuaded to screen out the obviously ill and to use measures which will reduce the chances of prolonged "bad" trips, this may serve as a bridge for further communication, since we know they are concerned about these matters. Persuading them not to seek and use these substances or preventing them from obtaining them seems to me to be a more difficult matter.

QUESTION: I would ask Dr. Osmond about how many times his chronic users had used the drug?

**Dr. Osmond:** One of our subjects used LSD–25 seven times, the last trip about two months before testing; another used it about 20 times. Our sample is not quite so intrepid as Dr. Silverman's. One young man claimed to have used 100,000 micrograms [illegible] LSD–25 in about five months, interspersed with STP on several occasions; we tested him some weeks after this last trip.

**Dr. Meyer:** We've now heard from the scheduled morning speakers and the floor is open to general discussion. A great deal of new material has been presented; particularly dealing with the treatment of adverse reactions. Are there any comments in this area?

**Dr. Freedman:** I think I'll underwrite the fact that the chief abuse of LSD has been selling, propaganda, and the whole ambience around that. We all know this. I also think that you in Government should not get into a position where you are the Vatican adjudicatory of all proper therapeutic procedures. You don't have to be. It's one thing to say, "Look, this chlorpromazine can be complicating; some people use it successfully, some do not. There are problems. Some people report amytal or chlordiazepoxide as effective." I think that the treatment community needs to know these facts because part of the reason the hippies move away from us is that they are greeted by a combination of ignorance and the tradition in psychiatry that we know everything before we've learned anything. This does not mean that you have to be in a position where you've got to deliver the latest authoritative word. It's a matter of style here.

**Dr. Joffe:** With respect to what Dr. Freedman just said and to what Dr. Smith said before, I'd like to make a plea on our behalf and show what we are doing. The gap between the hippie community and the establishment is great, but not any greater than between the Bureau of Narcotics and Dangerous Drugs and everybody else. With this as a given, I must depend upon those of you who are in contact with drug using groups to be the intermediaries to furnish information both ways. Anytime any of you learn of a new compound, please send it to me and I will get it analyzed, the way we got STP identified. The treating physicians need this information and the Bureau of Narcotics and Dangerous Drugs should have this information. Most of all it is crucial to the afflicted that we know as much as possible about their affliction. In the interest of the public health it is imperative that we obtain this information while guaranteeing total confidentiality to your sources.

QUESTION: Would you elaborate on your statement with regard to the identification of black-market materials?

**Dr. Joffe:** Yes. Sandoz has said that since they are no longer involved with LSD–25, they cannot analyze the substance. However, as far as the analysis of the material goes, we can do this. In addition, NIMH is supporting an investigator on the West Coast to develop methods for the identification of microgram quantities of psychotropic drugs (in particular, hallucinogenic drugs which are involved in epidemics of drug abuse).[31] We hope that this laboratory will be able to identify unknown black-market compounds. Thus we will have two laboratories, and NIMH can serve as intermediary, thus preserving confidentiality. There are also certain regional laboratories of the Bureau of Narcotics and Dangerous Drugs which are very competent to do this type of analysis.

QUESTION: Would a scientist be in jeopardy for possession of the black-market materials?

**Dr. Joffe:** I'm sorry; I don't know the answer to that.

**Dr. John Scigliano:** The Customs House Laboratory in Baltimore has expertise, and the Chief of the Laboratory has indicated a desire to cooperate in elucidating the composition of many of these agents. Thus, on the East Coast we have another resource for analysis which we can develop.

**Dr. Smith:** I'd like to introduce a new subject which concerns us in Haight-Ashbury. In our recent drug survey we found that the population has just about tried everything once. Thirty-three percent of our sample had at one time or other taken methamphetamine intravenously. The major drug problem in the Haight-Ashbury is the abuse of the amphetamines. We're seeing a very high incidence of post-LSD depression (presenting as a chronic depression in repeated users of this substance) suggesting that amphetamine abusers represent a certain segment that gets on to amphetamine abuse because of post-LSD depression. In this group, amphetamines serve as a kind of self-treatment for depression. When they stop taking the amphetamine, they're even more depressed. They then turn to higher doses and eventually to intravenous medication. This is one factor in amphetamine abuse relative to the particular subculture that we are working with. I would like to get some advice, on what Drs. Frosch, Ungerleider, and Ditman are doing with these post-LSD depressions. If possible I'd like them to discuss the problems of perceptual disturbances, recurrent hallucinosis, and other chronic disturbances associated with LSD usage.

**Dr. Ditman:** I have seen 50 or 60 post-LSD cases in treatment. Like Dr. Frosch, I am impressed that these cases do not respond to any treatment as well as you might expect, regardless of the diagnostic category that they are put in, whether it's anxiety, depression, or psychosis. Some of the cases that come in with the diagnosis of LSD-induced psychiatric complication often turn out to be people with problems that have existed prior to LSD ingestion, but LSD becomes the diagnosis or the excuse. I am thinking of a young man I saw yesterday who has been trying to make it as a rock and roll artist; he hasn't succeeded, and now he is using his LSD experience as the reason for his failure. He is depressed. It may be that LSD had a role in it. He said LSD made him recognize some of the things he has done wrong.

To summarize, I do not think that many of these are just LSD complications. LSD sometimes even has a minor role. Where LSD has had a major role, I am still very much perplexed as to what the treatment should be. I am impressed on a short-term basis with what can be done with sedatives, particularly with one of the longer-acting ones.

I would like to ask you one question, Dr. Smith. I keep hearing from patients about somebody who has had a "bad" trip and taken LSD again, to erase the after-effects of the bad experience with good results. I have heard of this a number of times, and wonder if this has become a treatment procedure in your group.

**Dr. Smith:** This is a very disturbing phenomenon in our community. There is a popular drug-myth associated with the Leary group that if you've had a "bad" trip, the thing to do is to go up again immediately to rescramble the circuits and get back on the beam. It has been our experience that this almost uniformly meets with disastrous results.

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[31] Craig, John C. School of Pharmacy, University of California, San Francisco, California. Microgram Identification of Psychotropic Drugs (1 RO1 MH 14321–01).

Getting back to my point about the post-LSD depressions, I would like to point to the low state of knowledge in the general medical community where many physicians are uniformly putting their patients on chlorpromazine. Frequently, they are treating post-LSD depressions with this drug. As you know, this treatment may actually worsen the depression. In fact, the only successful cases that I've had in our group are those taken off chlorpromazine by our staff. When the level of knowledge is so low among the medical community that they will prescribe daily doses of chlorpromazine for depression, then I think we've got a real problem.

However, in specific reply to your question, we focus on trying to convince the patients not to take LSD again. When they take LSD again without guidance, in approximately the same situation as during the first "bad" trip, they then have another bad reaction that further deepens the depression. In fact, some of the suicide attempts that we've had in our community have been a direct result of taking LSD again after having a "bad" trip.

**Dr. Jerome Levine:** I think this discussion underscores what I have said on several occasions. To confuse the picture, we've recently completed a collaborative depression study in which we have found that, on the whole, chlorpromazine is as good as imipramine in the treatment of depression; and that both drugs are better than placebo in treating patients with this symptomatology. This should shake up your conceptual system as it will shake up a number of the "more knowledgeable people in the community." It shook us up. My answer is that your long-term chronic depressions are the difficult ones whom you should try and route into treatment with some knowledgeable people who can offer them what is known, and who can offer them a way back to the ordinary community rather than offering them a pill which will reverse this process. I think each case must be treated by a competent treatment person, and that he will have to determine what the appropriate treatment is.

**Dr. Silverman:** To me the notion of LSD reaction is becoming as alien as the notion of schizophrenia has been to me for several years. There's no such thing as schizophrenia. I can show you that by showing you types of response patterns within the diagnostic category of schizophrenia that are so remarkably different from one another that normals who fit into a mid-range pattern resemble each of these types more than these discrepant schizophrenic-types resemble one another. In essence, when we look at these LSD types, we are looking at radically different modes of adjustment after the drug has been ingested. I feel certain that the drug treatment or other technique of choice that we use in the therapy of the patient experiencing panic or depression must depend upon the kind of reaction which follows LSD, and the particular personality or perceptual type underlying this reaction.

**Dr. Freedman:** I think we ought to remind ourselves about the depression that you are talking about. If you experience an order of insight or revelation, and the world suddenly looks quite startlingly different to you, then you have to integrate drab reality with drug-induced paradise. This could very easily set up the ground work for depression. There is also more than depression. There is the despair of the character disorder represented by these kids and its reinforcement in the groups that they are in. I've never been convinced—even without LSD in the picture—that we have done too well in psychiatry with the tools we have in treating this order of phenomenon (the character disorder) in young people. Back in the 50's Greenwich Village was full of chronic middle-aged dropouts who may have been pot smokers but certainly did not use LSD. Again, you've got to ask yourself what your therapeutic ambitions are, as well as what therapeutic skills, including group therapy, you can bring to bear.

The second thing is that in terms of long-term effects, I've seen a number of compensated schizophrenics who have what Bleuler called double registration. They live this way. I think the drug can give a relatively normal person this experience of double registration, of seeing two things at the same time. This could alter drastically the way these people now tend to perceive the world. Some people can adapt to it just as many schizophrenics have, and others cannot. I think we've got to respect the drug's power to do this, and, hence, to give a person a new task to deal with. This may be part of the long-term perceptual changes you've been talking about.

**Dr. Osmond:** That is a very good point, Dr. Freedman. I think we also have to remember that there is a very long history of this in the mystical literature. St. John of the Cross, and many others, give excellent accounts of it. There seems to be a contraction of the world after the divine revelation which produces great despair and sorrow in many people. There is also in the same literature a great deal of information as to what you do about it. I think that we might look at the actual way in which it was handled. While the experience of that time may not be applicable to our time, it's quite likely that the general responses they did observe are applicable today in a different context, using different ideas.

**Dr. Freedman:** I would like to address a question to everyone here. It was introduced by Dr. Osmond when he said that the alcoholics seem to do better after LSD. I have never seen an alcoholic who has had a bad effect due to LSD in terms of what we've been talking about. I've seen few, only one or two older people, who have had a bad effect after LSD and I've known a number of such people who are using LSD. These are older intellectuals, and certainly middle-aged people, very few of whom have gotten into trouble. It seems to me that this has something to do with age and the experiencing of alteration of consciousness that may be very important in determining whether or not a person has an untoward effect after LSD use. Certainly older people, perhaps also alcoholics, should have diminished reparative processes. If anything, they should be the ones who would suffer most, but apparently they don't, at least not in my clinical experience.

**Dr. Frosch:** I'd like to comment about taking LSD again to cure a "bad" trip. We've seen a number of patients who have taken other drugs after a "bad" trip. This other drug—marihuana, alcohol, or amphetamine—will sometimes precipitate a "bad" trip similar to the original LSD experience. We've also seen a few patients who have psychotic reactions to any drug they take. A number of people who come in with an amphetamine psychosis come back a few weeks later with an LSD psychosis. They may also have "bad" trips with marihuana. Drs. Freedman and Ungerleider have commented about age. We've seen a few older people, not terribly many, who have had "bad" trips. I'd like to know if anybody has seen people in the involutional period who have taken LSD and, if so, what the affective response is in such people.

**Dr. Freedman:** I've seen a few people, maybe a dozen or so in their 50's, who have taken LSD, and none of these that I can recall have had bad after-effects.

**Dr. Osmond:** About three years ago I saw the oldest man on record, as far as I know, who ever took it. He was 89, an old Australian who came to Abe Hoffer and said that he wished to do this. Abe told him that this was a very bad idea, that at his age he shouldn't be doing these things. The old gentleman said that he intended to; he had done everything in his life and he intended to do this. He said that if Abe wouldn't give it to him, he would go and get it from someone else. They inquired of his physician who saw no particular reason for his not doing so. Indeed he took it and had a truly remarkable experience; at one point he looked at the light and it suffused the room in a very wonderful manner. At the end of the time he came to Abe and said, "I am very grateful for this. This is the greatest moment of my life; I'm extremely happy. For all of my life I've been a convinced atheist, but in later years I've been rather doubtful about it. Now I know I was right all the time."

**Dr. Meyer:** I wonder if some of the people sitting on the sidelines, such as Dr. McGlothlin, Dr. Katz, and Dr. Pahnke who have had some experiences with the drug have some comments to make on some of the things that we have been hearing.

**Dr. Walter Pahnke:** I have two questions and a comment. First, regarding the age question. I've been treating dying cancer patients, and although our series is small so far, we have seen no adverse reactions to LSD under these controlled medical conditions. Dr. Silverman, when the people took 50 gamma under your experimental conditions how did their experiences correspond with those they had using black-market LSD?

**Dr. Silverman:** I would say that seven out of eight thought they had minimal psychedelic experiences.

**Dr. Pahnke:** Dr. Smith, if STP lasts for 30 to

72 hours, do these people not sleep for the whole time?

**Dr. Smith:** A majority of the patients do not sleep all the time. The popular statement is that under the influence of STP, a lot of them go into a trance-like state which they describe as sleep. They wake up and are still hallucinating. Although it seems highly unlikely that you can sleep with a heart rate of 120 and the other physical signs, they do describe the ability to sleep; but when they wake up they are still actively hallucinating.

**Dr. Osmond:** Klüver[32] describes one of his cases, a man who went to sleep one evening after a psychedelic experience and then woke up the next day with it still going strong.

**Dr. Pahnke:** In terms of what has developed with LSD abuse and the types of expertise needed from all different fields, and in terms of understanding LSD as a research tool, as a therapeutic agent, and as a social-anthropological phenomenon, the situation now begins to remind me of the whole area of narcotic drug addiction. The drugs are totally different. The predominant types of individuals who abuse these drugs are very different, but the way in which the community is responding to the phenomenon is very similar. This reminds me of a comment that Mitch Balter of the Psychopharmacology Division, NIMH, made after visiting Haight-Ashbury recently. He said that the culture there looks a lot more like a wino culture than he had expected. I think there is some similarity there, too, which again makes us think that we may have to bring our experience in dealing with these other types of phenomena to bear on this whole LSD issue.

**Dr. Meyer:** We turn now to the genetic area. Drs. Cohen and Hirschhorn might bring us up to date on their work.

**Dr. Maimon Cohen:** I should like to present additional *in vitro* data to supplement that reported in the recent *Science* paper,[33] and proceed to some *in vivo* experiments that have just been completed. After presentation of the data, Dr. Hirschhorn will discuss and interpret the possible significance of these findings. The use of a cytogenetic approach to the phenomenon of chromosome breakage by LSD is the adaptation of a method that has been used for some time in the screening of various exogenous agents. The basic *in vitro* approach is to expose normal leukocytes to the test agent while using untreated cultures from the same samples as controls. The system, for those of you who are not familiar with it, consists of stimulating white blood cells to divide in the culture, adding the test agent, arresting the cells at the metaphase stage of mitosis, and scoring chromosomal abnormalities.

The first observation, even before examining the chromosomes themselves, is to study the effect of the agent on the mitotic rate. Do the treated cultures differ from the controls in regard to the cell division? Figure 1 shows the results of such mitotic indices.[34] The treatments or the concentrations of LSD used ranged from 10 gamma per ml of culture to 0.001 gamma per ml. The mitotic rate in the control cultures was a bit over 6 percent, which is normal using our method. However, as you can see, with all of the dosages of LSD used, there were statistically significant suppressions of mitosis. The longer the drug was in contact with the cells, the greater the suppression of the mitotic rate. The data in these *in vitro* experiments were derived from three males and three females who had no known exposure to LSD, no recent radiation exposure, and no recent viral infections. The reason for these restrictions will be discussed later.

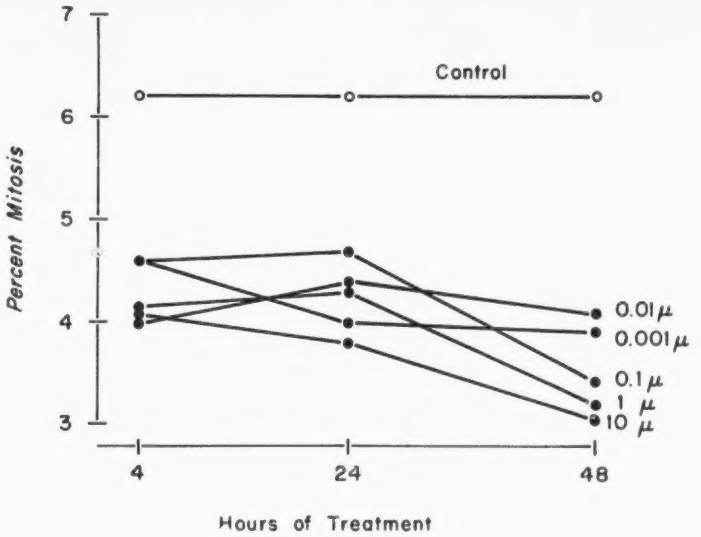

Figure 1.—*Effect of LSD on Mitotic Rates of Leukocytes Derived from 6 "Drug-Free" Controls.*

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[32] Klüver, see footnote 3, page 2.

[33] Cohen, see footnote 2, page 1.

[34] Figures 1–3 and tables 9–14 are reprinted with permission from the *New England Journal of Medicine* and the author, from the article *"In Vivo* and *in Vitro* Chromosomal Damage Induced by LSD-25," by Maimon M. Cohen, Kurt Hirshhorn, and William Frosch. *New England Journal of Medicine*, 277(20):1043–1049, November 16, 1967.

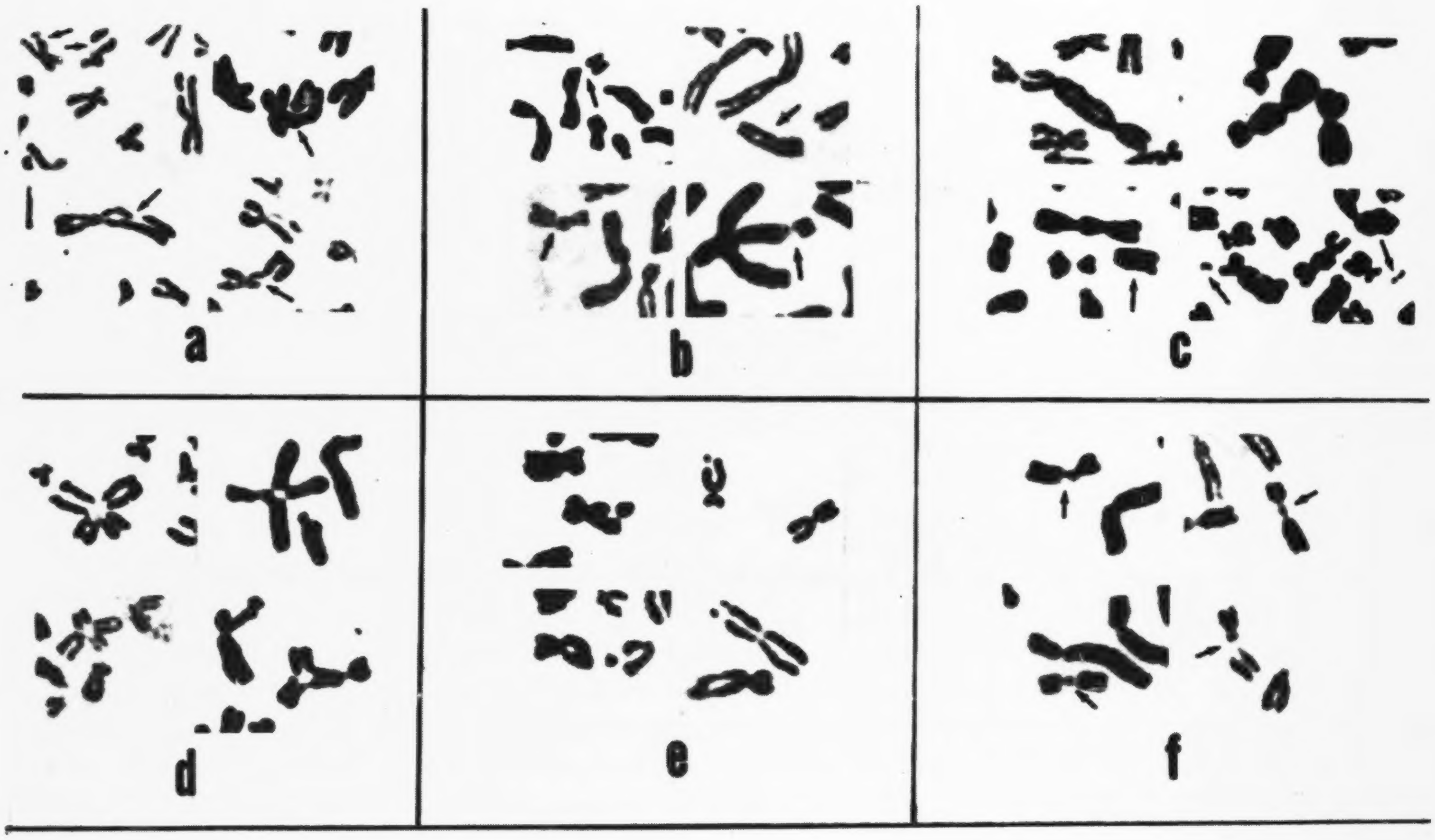

FIGURE 2.—*Types of Chromosomal Abnormalities Observed in Both the in Vitro Experiments and from the Leukocyte Cultures Derived from Drug "Users," Showing Chromatid Breaks (a), Isochromatid Breaks (b), Dicentric Chromosomes (c) (Arrows Indicate Acentric Fragments), Exchange Figures (d), Chromatid Breaks Giving Rise to Terminal Deletions and Acentric Fragments (e) and Attenuation and Breakage at the Secondary Constriction in Chromosome No. 9 (f).*

Figure 2 illustrates the types of chromosomal abnormalities that can be quantitated. Figure 2-a shows a simple type of break appearing as an area in which the chromatid or the chromatin material is nonstaining, with a nonalignment of the distal portion of the chromatid. In other words, the continuity of the chromatid is disrupted. The criterion of nonalignment is used to define a break—a distal nonalignment of the chromatid. A gap is a nonstaining portion of the chromosome, which apparently looks broken, but the remainder of the chromosome arm is still normally aligned. This type of lesion would not be scored as an abnormality. The frequencies of abnormalities included in the study are those breaks, as defined by the alignment-nonalignment criterion. A chromatid break occurs only in one chromatid of the two. An isochromatid break or chromosome break occurs in both chromatids, giving rise to a double fragment (Figure 2-b).

QUESTION: Could you point out a normal one?

**Dr. Cohen:** Here is a normal chromosome with its centromere. This structure attaches to the spindle during mitosis and the chromatids separate to the two daughter cells. Figure 2-c represents dicentric chromosomes, e.g., a chromosome, with two constrictions or two centromeres with the occurrence of acentric fragments. This has some interest as far as LSD itself is concerned because this aberration isn't seen too frequently with other drugs.

An attempt to localize the breaks to given areas of the chromosomes indicated that a large number of terminal breaks occurred toward the ends of the chromosome arm (Figure 2-e). If such breaks occur in two chromosomes in a given cell and these two chromosomes are in close proximity to each other and re-heal through the broken ends, this would yield an increased frequency of dicentric chromosomes as observed. I have not seen this phenomenon with several of the other agents that have been screened this way. However, Dr. Hirschhorn has seen a similar phenomenon with $SV_{40}$ infection. $SV_{40}$ is an oncogenic virus which induces "end-to-end" associations and dicentric chromosomes from terminal breaks. The next type of structural rearrangement of the so called quadriradial figures, or triradial figures, most probably involve breakage between two chromosomes and exchange of genetic material (Figure 2-d). Figure 2-f shows a particular area of certain chromosomes which is affected. These are secondary constriction regions, which seem to be not only affected by LSD but by a whole host of exogenous agents. These seem to be particularly vulnerable areas of the chromosomes.

Table 9 is a composite of the *in vitro* break frequencies observed. Again, let me remind you that this is the pooled study from six individuals. There were no significant differences in frequencies of response either by sex or individuals, so these figures were pooled. The control rate which you see at the bottom, the 0.039, refers to breaks per cell, or if you look at figures outside the parenthesis, the number of breaks divided by the number of cells examined (65/1680). This control figure is within the range normally observed in my laboratory; Dr. Hungerford, Dr. Warkany, and the other cytogeneticists who have had experience with chromosome breakage will bear me out. Control figures range between 0.0 to 5 or 6 percent.

**Table 9.—DISTRIBUTION OF CHROMOSOMAL BREAKS INDUCED IN CULTURED HUMAN LEUKOCYTES BY VARIOUS DOSAGES AND EXPOSURE TIMES TO LSD–25.***

| HR. BEFORE HARVEST | DISTRIBUTION OF BREAKS WITH DOSAGE INDICATED | | | | |
|---|---|---|---|---|---|
| | *10 μg/ml* | *1 μg/ml* | *0.1 μg/ml* | *0.01 μg/ml* | *0.001 μg/ml* |
| 48 | 50/398<br>(12.6) | 30/390<br>(7.7) | 77/439<br>(17.5) | 55/515<br>(10.7) | 53/425<br>(12.5) |
| 24 | 61/530<br>(11.5) | 93/587<br>(15.8) | 73/560<br>(13.0) | 81/527<br>(15.4) | 57/529<br>(10.8) |
| 4 | 95/554<br>(17.1) | 62/587<br>(10.6)* | 76/582<br>(13.1) | 81/534<br>(15.2) | 65/578<br>(11.2) |
| Control | 65/1680 = (3.9) | | | | |

*Figures in parentheses denote % of cells with breaks.

QUESTION: How does your first figure differ from this table?

**Dr. Cohen:** The first figure describes mitotic rate. We are now discussing chromosomal breakage. Table 10 depicts the uniformity or non-uniformity of the action of the drug across the chromosomes. The question is—do all of the chromosomes react in the same way or is there an apparent non-random distribution of chromosome breaks? This analysis is done on the basis of length of the chromosomes by calculating the length of each chromosome or chromosome group. On this basis, it is possible to calculate the expected numbers of breaks in each chromosome. It is quite obvious from this distribution and Chi-Square test that LSD does *not break* the chromosomes uniformly. This is not peculiar or unique to LSD; practically every agent with the exception of radiation yields a non-uniform distribution.

**Table 10.—DISTRIBUTION OF CHROMOSOME BREAKS ACCORDING TO INDIVIDUALLY IDENTIFIABLE CHROMOSOMES OR CHROMOSOME GROUPS.**

| | CHROMOSOME GROUP | | | | | | | | | | UNIDENTIFIABLE FRAGMENTS & BREAKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | A1 | A2 | A3 | B | C | D | E | F | G | TOTALS | |
| Observed | 154 | 119 | 41 | 93 | 420 | 45 | 41 | 11 | 6 | 930 | 79 |
| Expected | 80.82 | 75.70 | 63.43 | 113.0 | 346.52 | 93.65 | 80.26 | 42.22 | 34.32 | 929.9 | |
| $\chi^2$ | 66.26 | 24.77 | 7.93 | 3.54 | 15.58 | 25.27 | 19.20 | 23.09 | 23.37 | 209.01 | |

df = 8; $p < 0.001$

Figure 3 shows an attempt to localize further the breaks within given chromosomes. It appears that in many of the chromosomes or chromosomal groups the centromere regions are extremely sensitive to LSD. Outside of this there are other areas which show a piling up, so to speak, of the chromosomal breaks, and this again is not unique to LSD. These vulnerable areas are the secondary constrictions, heterochromatic regions, which apparently respond to many types of insults more readily than the euchromatic or darkly-staining regions of the chromosomes.

So much for the *in vitro* studies. We have recently completed a collaborative effort with Dr. Frosch and Dr. Hirschhorn, and I will describe

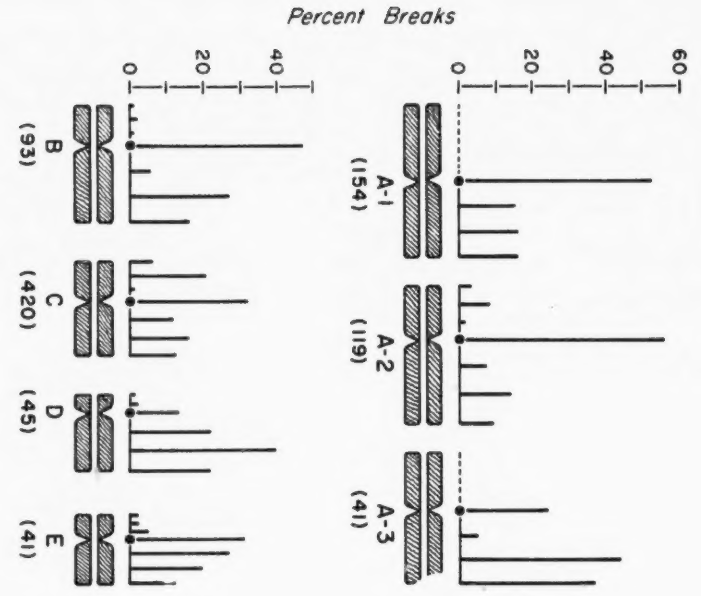

**Figure 3.**—*Distribution of Chromosomal Breaks within Given Chromosomes or Chromosomal Groups (Figures in Parentheses Indicate the Number of Breaks).*

the design of this experiment briefly. The series consisted of 18 LSD users and was derived from Dr. Frosch's patients at Bellevue Hospital. Dr. Frosch had blood samples drawn in tubes at Bellevue; the coded tubes were given to Dr. Hirschhorn who propagated the cultures at Mt. Sinai Hospital and recoded the microscope slides. There were two cover slips to a slide, no two cover slips on the same slide coming from the same individual. I received the coded slides, and carried out the analysis for chromosomal damage. Table 11 shows the control subjects. There are 14 listed on this particular table, two of whom I think we are justified in removing from the study. These two females showed high rates of chromosomal breakage, but within 24 hours after bleeding for the cultures, both came down with diarrhea, vomiting, and high fever; a picture compatible with the diagnosis of a viral infection. Virus infections are known to cause increased chromosomal breaks, but this damage is of a transient nature. We examined these individuals ten days later and the breaks had disappeared. These two girls have been used for controls in other experiments as well, and their break rates are within the normal frequencies. The remainder of the controls exhibited chromosomal breakage rates ranging anywhere from 2 to 5.5 percent, which is within the normal range for individuals without drug ingestion.

### Table 11.—CHROMOSOMAL DAMAGE IN SUBJECTS USED AS NORMAL "DRUG-FREE" CONTROLS.

| Case No. | Age yr. | Sex | Per Cent Breaks* |
|---|---|---|---|
| 5 | 35 | Male | 5.0 ( 5/ 100) |
| 17 | 39 | Female | 4.9 ( 9/ 182) |
| 19 | 29 | Male | 5.5 ( 11/ 200) |
| 24 | 23 | Male | 4.3 ( 13/ 300) |
| 25 | 28 | Female | 4.1 ( 13/ 314) |
| 27 | 26 | Female | 4.5 ( 9/ 200) |
| 30 | 23 | Male | 2.8 ( 7/ 250) |
| 33 | 24 | Male | 2.3 ( 6/ 257) |
| 35 | 23 | Male | 5.0 ( 11/ 221) |
| 40 | 55 | Male | 2.0 ( 4/ 200) |
| 41 | 23 | Male | 3.0 ( 6/ 200) |
| 42 | 22 | Male | 3.2 ( 8/ 250) |
| | | | 3.8 (102/2674) |
| 4 | 37 | Female | 31.0† ( 31/ 100) |
| 13 | 23 | Female | 14.0† ( 28/ 200) |

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*** Figures in parentheses denote number of breaks per cells investigated.**

**† Viral infection, with high fever & diarrhea, developed within 24 hr. of bleeding.**

Table 12 shows the data from LSD patients. The subjects are listed in descending order of the number of doses or the number of trips, and since these are all from Dr. Frosch's records, he will have to defend the numbers involved—300, 200, and so forth. The next-to-last column contains the chromosome-break data. There is a wide range in the responses of these individuals as far as chromosomal breakage is concerned. Several were well within the control rate of 5 to 6 percent, but the vast majority of them were two to four times higher than the controls. Again, to emphasize the point made repeatedly this morning and to quote Dr. Frosch's phrase, "Most of the LSD users are inveterate experimenters with other drugs," you can see from the last column of this table, the other drugs used—A's are the amphetamines, B's are the barbiturates, and so forth. All of these individuals had ingested some other drugs. Of course this is a confounding parameter in the whole study. What effect, if any, do these other drugs have on chromosome breakage, and, if *in vivo*, is this due to LSD itself? To this end, Dr. Frosch collected a group of patients who were not taking LSD but who were ingesting some of the other drugs.

| Case No. | Age | Sex | No. of Doses | Interval between Last Dose & Bleeding | Per Cent Breaks | Other Drugs According to History* |
|---|---|---|---|---|---|---|
| | *yr.* | | | | | |
| 10 | 19 | Male | 300 | 2 wk. | 9.0 ( 18/200) | A,M,O,P |
| 3 | 24 | Male | 200 | 1 mo. | 9.8 ( 28/285) | A,H,M,O |
| 34 | 22 | Male | 100 | 1 mo. | 25.1 ( 44/175) | A,H |
| 9 | 28 | Female | 100 | 2 mo. | 11.0 ( 22/200)† | A,B,C,H,M,P |
| 22 | 29 | Female | 30-60 | 1 mo. | 15.3 ( 46/300) | A,M,P |
| 29 | 22 | Male | 50 | 1 mo. | 5.5 ( 10/183) | H,M,O,P |
| 7 | 24 | Male | 50 | 7 mo. | 11.6 ( 29/250) | A,B,C,H,P |
| 32 | 20 | Male | 35 | 1 mo. | 12.0 ( 30/250) | A,B |
| 6 | 19 | Male | 20-25 | 4 mo. | 10.3 ( 19/184) | A,H,M,P‡ |
| 20 | 22 | Male | 15-20 | 4 mo. | 12.6 ( 35/278) | A,H,M |
| 37 | 52 | Male | 15 | 8 mo. | 13.0 ( 39/300) | P |
| 14 | 25 | Female | 15 | 1 mo. | 20.3 ( 61/300) | A,H,M |
| 36 | 26 | Male | 15 | 1 mo. | 22.0 ( 58/264) | A,H,M,P |
| 39 | 23 | Male | 6 | 7 mo. | 24.0 ( 36/150) | A,H,M,O,P |
| 2 | 21 | Female | 4 | 2 mo. | 6.4 ( 5/ 78) | A,B,C,H,M,O |
| 26 | 20 | Female | 4 | 1 mo. | 14.0 ( 42/300) | M |
| 38 | 22 | Male | 3 | 6 mo. | 9.8 ( 28/285) | A,H,M |
| 28 | 21 | Female | 2 | 1 mo. | 5.3 ( 16/300)† | A,C,M,P‡ |
| | | | | | 13.2 (566/4282) | |

*A indicates amphetamines, B barbiturates, C cocaine, H hallucinogens, M marijuana, O opiates, & P phenothiazines.

†Low dose (50-100 μg).

‡Phenothiazine at time of bleeding.

**Table 12.—CHROMOSOMAL DAMAGE IN PATIENTS INGESTING LSD.**

QUESTION: Is there any relationship to the doses?

**Dr. Cohen:** No, as far as we could ascertain, there was no apparent relationship between the number of doses, the time of exposure of the last dose prior to the time of bleeding, other drugs, frequency of other drug use, and the rate of chromosome damage.

QUESTION: What about individual dosages?

**Dr. Cohen:** These were all between 300 and 600 micrograms.

**Dr. Frosch:** They mostly claim to take 500 micrograms. A few people who were asked claimed only to have taken low doses, 50 to 100 micrograms. It's important to remember that this was a black-market calculation.

One of the persons who took the drug the longest time ago, seven months, had one of the highest break rates, 24 percent.

**Dr. Cohen:** Let me modify a statement I made earlier. These are not all of Dr. Frosch's patients. The one individual who is 52 years old, midway down the table, was the patient originally described in the *Science* paper.[35] This patient was a schizophrenic who was on non-black-market LSD therapy for a four-year period. We took his blood sample eight months after his last dose and he still had 13 percent chromosome breaks, but the important thing is that he also showed the structural rearrangements.

Table 13 will show the so-called LSD drug-positive controls. There were six subjects and the first three individuals who were on chlorpromazine at the time of bleeding showed chromosomal breakage as high, if not higher, than the LSD users. The fact that these individuals were on chlorpromazine at the time of bleeding may be significant. This appears to be akin to the transient virus infection. We are now in the process of setting up experiments to test chlorpromazine and similar tranquilizers *in vitro* first and secondly *in vivo* with a series of patients to be examined before, during, and after chlorpromazine treatment.

Some of you have undoubtedly seen the press coverage of the National Foundation-March of Dimes meeting that was held several weeks ago (September 1967) in New York at which chlordiazepoxide and diazepam were also implicated in chromosome damage. These were results by Dr. Morton Stenchever from Western Reserve University, who is interested in these drugs when used during pregnancy. His results

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[35] Cohen, see footnote 2, page 1.

## Table 13.—CHROMOSOMAL DAMAGE IN PATIENTS INGESTING DRUGS OTHER THAN LSD.

| Case No. | Age | Sex | Race | Drugs | Per Cent Breaks |
|---|---|---|---|---|---|
|  | *yr.* |  |  |  |  |
| 8 | 20 | Male | W | Chlorpromazine, 200 mg/day, for 1 mo. until day of bleeding | 17.4 (34/195) |
| 16 | 34 | Female | N | M* – 10-yr. duration; chlorpromazine, 50 mg/day for 2 days until day of bleeding. | 21.5 (43/200) |
| 31 | 30 | Male | N | Chlorpromazine, 200 mg/day, for 3 wk. until day of bleeding. | 13.7 (28/205) |
| 18 | 31 | Male | W | A* – 4-yr. period up to 1 gm/day (last dose 2 wk. before bleeding); 0* – 6 yr.; M* – 15 yr.; B* – intermittent. | 9.0 (18/200) |
| 21 | 9 | Male | N | Diphenhydramine, 100 mg/day for 1 mo. up to time of bleeding. | 10.0 (26/261) |
| 23 | 9 | Male | N | Chlorpromazine & thioridazine for 1½ yr. up to 1 mo. before bleeding; diphenhydramine for 1 wk. before bleeding; patient addicted to opiates at birth – exposed throughout pregnancy. | 4.0 (12/300) |

* See key to Table 12 for abbreviations.

are from *in vitro* investigations at this point. He had not yet actually looked at the *in vivo* situation. I think probably one of the more interesting points of the *in vivo* LSD study is shown in the next table. We were able to study four children who were exposed to LSD *in utero* (Table 14). The last two children in this series were carried by one mother who, as Dr. Frosch pointed out, was receiving low dosages. According to the pregnancy history, she took the LSD late in pregnancy as opposed to the first two who took it earlier in pregnancy, in the second trimester. The two children, exposed in the second trimester to LSD with the normal dose (500 gamma), showed significantly higher break rates than the other two (exposed late in pregnancy), and in these children as well, we saw morphologic rearrangements of the chromosomes. One child is two and one-half years old, and adding the time *in utero,* showed significant breakage approximately three years after the single dose. I may make a comment later on this point when we talk about teratogenicity.

QUESTION: What was the nutritional status?

## Table 14.—CHROMOSOMAL DAMAGE IN OFFSPRING OF MOTHERS WHO INGESTED LSD DURING PREGNANCY.

| Case No. | No. of Mothers | Age | Sex | No. of Doses in Utero | Per Cent Breaks | Other Drugs Used in Utero* |
|---|---|---|---|---|---|---|
| 1 | 2 | 11 mo. | Female | 4 | 19.0 ( 57/ 300) | A.C.M |
| 15 | 14 | 2½ yr. | Male | 1 | 13.0 ( 39/ 300) | – |
| 12 | 9† | 5½ yr. | Female | 2 | 7.5 ( 15/ 200) | M |
| 11 | 9† | 2 mo. | Male | 4 | 4.0 ( 8/ 200) | C.M |
|  |  |  |  |  | 11.9 (119/1000) |  |

* See key to Table 12 for abbreviations

† Low dose (50–100 µg).

**Dr. Frosch:** It varied. Overall, I would say it was certainly not a malnourished group.

**Dr. Meyer:** Dr. Hirschhorn, we are now anxious to hear your comments.

**Dr. Kurt Hirschhorn:** There are just a few comments I want to make on the interpretation and possible significance of these data. I think the first point (which I will come back to later) is that we did find a variation in apparent susceptibility to chromosome breaks. I think some of the previous discussion about psychological reactions was hedging around this point to some extent, and all I would do at this particular time is to remind you of a rapidly growing field that the pharmacologists here will be acquainted with, the field of pharmacogenetics. One must remember to account for individual differences before making general statements about anything, since these individual differences may in fact be on a genetic basis. With reference to the potential dangers of the type of chromosome breakage that we have seen, the particularly important aberrations are the ones which result in rearrangements, that is, chromatid exchanges and dicentrics.

Let me first emphasize that we have no evidence at this time that the dangers I'm going to talk about do actually exist in the human population. This question can only be settled by a large epidemiological study, which I hope can be put into effect with the rather large population available at this time. The potential dangers are the following: (a) To the individual himself. It is well established and I think it will be discussed later that chromosome breakage and rearrangement induced either by radiation or spontaneously occurring in certain genetic diseases, such as Fanconi's anemia, and so on, are associated with quite a high incidence of leukemia and other neoplasms. This will have to be looked into in the future. (b) To the unborn child who is exposed to the drug *in utero*. There are now three studies, one by Alexander in rats,[36] one by Auerbach in mice,[37] and, perhaps the best, by Geber in hamsters,[38] that have demonstrated the teratogenicity of this drug if given at a particular point in time during the pregnancy. Again this is something that will have to be studied in man. It must be pointed out that most of such chromosome damage is probably so severe that it will not result in teratogenesis but rather in spontaneous abortions, possibly quite early in pregnancy; here again the epidemiological study is the one that is important. (c) The genetic damage to future generations. The important aspect of this is the chromosome rearrangement, which results in a so-called translocation, in other words, a new chromosome consisting of two parts of two different chromosomes. There results from this a high risk of having abnormal children or children who will die *in utero,* in the next generation, or of producing carriers of such translocations who will show such abnormalities in the third generation. Whether this is true or not will depend to a great extent on the presence or absence of these chromosomal rearrangements in the cells that are going to make sperm and eggs. We now have testicular biopsies planned in order to try this, to see whether the germ cells carry the damage. There is an analogy with drugs called streptonigrin and mitomycin C, both of which produce effects on chromosomes quite similar to those produced by LSD. There is now evidence that in the germ cells there is the same kind of damage as that produced by streptonigrin; whether LSD does this, I don't know as yet. Preliminary data from the laboratories of Cohen and Philip [39-40] indicate that the germ cells of LSD-treated mice do carry the breaks and rearrangements.

The next point I want to discuss is the question of mechanisms. Chromosomes can probably be broken by a variety of mechanisms, possibly by direct damage to the chromosome as by ionizing radiation, possibly by way of cytoplasmic enzyme release. This has been postulated for some of the agents, including perhaps some of the viruses. Another possible mechanism is by inhibiting the healing of broken chromosomes. Breakage probably occurs normally all the time, but the chromosomes heal immediately. With this in mind I now begin to wonder whether LSD itself is breaking the chromosomes or whether perhaps it has some metabolic effect on the cell (possibly by way of serotonin metabolism, or by one of its metabolites, which in turn either unstabilizes the lysosomes which contain destructive enzymes that could break chromosomes) or alternatively interferes with the healing process that normally occurs in preventing permanent chromosomal damage in normal individuals.

Let me for a moment come back to the question of individual differences. We now have genetic evidence that some people are more susceptible to chromosome breakage than others, some to an extremely great extent. I think this too will have to be looked into very carefully. If one does find that there are some individuals who are susceptible and others who are not, I think that we will find here the clue as to what is going on. I would also urge you in terms of the psychiatrically-oriented studies to look at this problem in a similar way; that is, your clue may come by comparing reactors to nonreactors, rather than by comparing LSD takers to normals.

**Dr. Frosch:** I'd like to add two clinical notes to this study: (a) In this patient sample there was no correlation that I could discover between chromosome breaks and the presence or absence of overt behavioral disturbance. (b) The physical and psychological examination of these four children has not as yet revealed any gross physical, behavioral, or mental abnormality. However, they are very young and it is very difficult to do accurate testing.

QUESTION: Can you demonstrate this in animals, and if so, don't you have a quick way of finding out about the damage?

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[36] Alexander, G.J.; Miles, B.E.; Gold, G.M.; et al. LSD: injection early in pregnancy produces abnormalities in offspring of rats. *Science,* 157:459–460, July 28, 1967.

[37] Auerbach, R., and Rugowski, J.A. Lysergic Acid Diethylamide: effect on embryos. *Science,* 157:1325–1326, September 15, 1967.

[38] Geber, W.F. Congenital malformations induced by Mescaline, Lysergic Acid Diethylamide, and Bromolysergic Acid in the hamster. *Science,* 158:265–266, October 13, 1967.

[39] Cohen, M.M., and Mukherjee, A.B. Meiotic chromosome damage induced by LSD-25. *Nature,* 219:1072–1074, September 7, 1968.

[40] Skakkebaek, N.E.; Philip, J.; and Rafaelsen, O.J. LSD in mice—abnormalities in meiotic chromosomes. *Science,* 160: 1246–1248, June 14, 1968.

**Dr. Hirschhorn:** Chromosome studies are now being done in animals, but the results are not yet known. Such studies have been done in animals with a variety of other drugs producing similar chromosome breaks, but let me again warn of trying to derive information purely from animal studies; it has been done, but such interpretation is fraught with great danger. In terms of teratogenicity, I am sure that Dr. Warkany, who is probably the leading expert in this field, would bear me out in saying that if aspirin and thalidomide both had been subjected to animal tests before being put on the market, thalidomide would much more likely have been put on the market than aspirin.

**Dr. Freedman:** Could I just inject a controversial note. I am dismayed at the lack of controls before this was published. You've still got a lot of interesting work ahead of you.

**Dr. Cohen:** As far as the controls in the *in vitro* study are concerned, I think the proper controls are there. The cells were from identical blood samples drawn from the same individuals and then split into treated and untreated groups. This is the only type of comparison you can make in this particular type of situation; therefore, as far as the *in vitro* experiments are concerned, I think that there were adequate controls; these are replicate samples, one treated and one not. The control rates which we got compare well with control rates gotten for untreated cultures in any cytogenetic laboratory engaged in chromosomal studies.

**Dr. DiPaolo:** What about buccal smears?

**Dr. Cohen:** Buccal smears? They are good for distinguishing males from females, but they are not going to help a bit in this particular situation.

As far as *in vivo* system is concerned, then I admit we really do have a problem with controls except for the people who were not exposed to the drug, who were the overall controls for the whole group. I will grant you that this is a problem. They are not the ultimate control, but they were the best control that we could find. I don't know what better control you can ask for. I'm open to all suggestions of how better to control these things.

While I have the microphone I would like to read one sentence from a letter that I received yesterday. It is from a physician at the University of Iowa, in the Department of Obstetrics and Gynecology, and regards a recent fetus with a phocomelia anomaly. ". . . the mother and father were on daily doses of LSD prior to pregnancy and during the first three months. The mother, father, and baby exhibited the typical chromosome breaks." There is another observation.

**Dr. R. Miller:** I have two questions. First, it seems to me that LSD does produce a tremendous fright in some people; maybe this experience is releasing a whole lot of things that cause these breakages. It seems that control studies comparing those people who have very rough experiences and those who don't might be in order. Secondly, what do these abberrations in the chromosomes relate to, other than some drug that might have been taken? In other words, if you find a high incidence of leukemia, what meaning does that have?

**Dr. Hirschhorn:** In answer to the first question, there was no apparent correlation between whether they had a "bad" trip, a "good" trip, or otherwise. In terms of the second question, this is exactly what I was getting at; we don't know. All we know is that with similar chromosome breaks after radiation there is a higher incidence of leukemia; with similar chromosome breaks with patients with increased susceptibility to breaks there is a higher incidence of leukemia. With the same kind of chromosome breaks caused by other drugs there is a higher rate of abortion and of a variety of other things. With regard to LSD, we only know one thing: teratogenesis occurs in some animals when LSD is administered during certain times of pregnancy. What the story is in man can only be derived from a large epidemiological study.

**Dr. Meyer:** Do you know what the rates of breakage are in the community? In other words, if you have a high rate of breakage, you may have some problems in assessing the cause and effect or other relationship between high rates of breakage and leukemia.

**Dr. Hirschhorn:** What "community"?

**Dr. Meyer:** In the total population.

**Dr. Hirschhorn:** Yes we do. And that is around 4 percent, and this has been consistent.

**Dr. Meyer:** We can now go on to Dr. Hungerford's presentation.

**Dr. David Hungerford:** I'd like to say that the largest single portion of this work was done by Dr. Kenneth Taylor who is in the Biology Department of San Diego State College and was in my laboratory for a year on a special NIH Fellowship. Four other cytologists, including myself, were involved.[41] Dr. Shagass has already recounted to you the opportunity we had to study his patients. It arose last April just after Dr. Cohen's paper appeared in *Science*[42] and for that reason and because there was a prospect of doing an almost completely prospective study, we set out to do this. We have so far looked at four patients. They were sampled in general three times for each dose and they received three doses per course of treatment. They were also sampled on follow-ups. If you look at the tables you can see this. A good place to start is with the classification of chromosome abnormalities. It shows our scoring methods and criteria, which are very much like Dr. Cohen's.

### CLASSIFICATION OF CHROMOSOME ABNORMALITIES

A. No structural abnormality
- 1. Normal diploid
- 2. Hypodiploid or hyperdiploid
- 3. Polyploid
  - a) Triploid or tetraploid, or near triploid or near tetraploid
  - b) Endoreduplication

B. Gaps or breaks
- 1. Chromatid gap—(non-staining region in one chromatid)
- 2. Chromatid break—(non-alignment or axial displacement of broken ends)
- 3. Isochromatid gap—(non-staining region at same position in both chromatids)
- 4. Isochromatid break—(non-alignment or axial displacement of broken ends, break point at same position in both chromatids)

(Gap is a region entirely or partially achromatic and with or without constriction)

C. Other structural abnormalities
- 1. Acentric fragments, dicentrics, rings, multiradials-(classically regarded as unstable, liable to be lost or to undergo further change at mitosis)
- 2. One or more morphologically abnormal chromosomes resulting from multiple breaks leading to inversions, deletions, or translocations-(regarded as stable at mitosis)

These definitions were derived primarily from:

Jacobs, P.A.; Brunton, M.; and Court-Brown, W.M. Cytogenetic studies in leukocytes on the general population: subjects of ages 65 years and more. *Annals of Human Genetics*, 27:353–365, June 1964.

Other discussions of classification of aberrations are in:

Evans, H.J. Chromosome aberrations induced by ionizing radiations. *International Review of Cytology*, 13:221–321, 1962.

Swift, M.R., and Hirschhorn, K. Fanconi's Anemia: inherited susceptibility to chromosome breakage in various tissues. *Annals of Internal Medicine*, 65:496–503, 1966.

Chicago Conference: Standardization in Human Cytogenetics. *Birth Defects: Original Article Series*. Volume 2. New York: The National Foundation-March of Dimes, December 1966.

We have to begin with two controls (see Table 15) which were matched initially for age, sex, and sampling interval; the same scoring procedures were followed for them. It's interesting in this respect that the younger patient shows some of the effects of prior exposure to diagnostic radiation. We knew this when we started but neither he nor we knew how much radiation he had had, and you can see that it is considerably elevated in comparison to the 35-year-old control in the second row. He had at least one consistent chromosome change, a clone of cells in which there was a pericentric inversion.

If we turn to Table 16, we can see the frequencies of breaks plus the more serious kinds of rearrangement, including those which are unstable in subsequent mitosis. To interpret this table briefly for you: the frequencies are numbers of rearrangements over number of cells in which these have occurred. The items in parentheses are the total number of metaphases in each sample. If we sum the numerator of these frequencies across rows, we end up with, in the first case, 23 over 300 cells, which gives us 7.7 percent, etc., down.

Table 17 shows the same cells. Here we make an attempt to maximize the effect, if any, of LSD. We have included also the less serious aberrations, of types indicated as items B.1. and B.3. in the classification, which give a little bit higher percentages, and in both cases the percentages in the last column should be compared for three of the four patients with the pre-LSD samples in table 17 column 1; maximizing the data, we have 8 percent versus 9.3, 8 per-

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[41] Hungerford, D.A.; Taylor, K.M.; and Shagass, C. Cytogenetic effects of LSD-25 therapy in man. *JAMA*, 206: 2287–2291, December 2, 1968.

[42] Cohen, see footnote 2, page 1.

### Table 15.—CONTROLS

Frequencies of Structural Rearrangement of Chromosomes/Cells Involved; and Total Chromosome Aberrations/Cells Involved

| Case | | | | Cells Studied | Aberrant Cells |
|---|---|---|---|---|---|
| 28 yr. old control 544H | 8/1/67<br>7/6; 13/12<br>(100) | 8/8/67<br>To be studied | 8/22/67<br>2/2; 9/9<br>(100) | 200 | 21/200=10.5% |
| 35 yr. old control 545H | 8/28/67*<br>0; 5/5<br>(100) | 9/5/67*<br>0; 5/4<br>(100) | 9/18/67*<br>0; 4/4<br>(100) | 300 | 13/300=4.3% |
| | | | | 500 | |

Numbers in parentheses are total number of metaphases studied per sample.

*48 hour and 72 hour intervals in culture; all others 72 hour.

N.B. 544H had diagnostic X-rays to leg and spine 1952–54 and 1960. Clone is present with pericentric inversion in one chromosome #2.

cent versus 8.7, and 10 percent versus 8.2. These can be compared with the controls in table 15, where we got 10.5 percent for the irradiated control and 4.3 percent for the unirradiated control.

I should say that the statistical analyses have not yet been done. This is one thing that Dr. Taylor is undertaking at the moment. We all think that if there is any significance here it is borderline.

COMMENT: Well, this is an interesting set of data to compare with the results of Drs. Cohen and Hirschhorn[43] and with Drs. Irwin and Egozcue.[44]

**Dr. Hungerford:** I do not think that we necessarily have real discrepancies here; we are dealing with two different kinds of material, and there is some question about the integrity of the compound that the hippies are taking. I think one could draw a little bit of reassurance from the therapeutic experiences, with pharmaceutical-grade LSD, by physicians, but there seems to be a clear need to investigate the nature of possible contaminants in illicit batches and their effects specifically on chromosomes.

I would like to turn briefly to the leukemia question. Dr. Egozcue[45] has found in some of this material a minute chromosome, which he thinks is like the Philadelphia (Ph$^{1}$) chromosome found in most cases of chronic granulocytic leukemia. The Ph$^{1}$ is about 60 percent of a normal small acrocentric. We have done a little bit of cytophotometric work on this abnormal chromosome and have found that about 40 percent of the DNA is gone. I think that Dr. Egozcue's chromosome is a little too small, and that the construction that is being put on this in the press is misleading.

**Dr. Cohen:** I don't think there's any doubt about the last point made by Dr. Hungerford that the chromosome referred to by Dr. Egozcue is Ph$^{1}$. Those of us who saw his *Science* article[46] would have a great deal of difficulty telling what it really was, and I don't think it was all his fault, for the photographic plate was a very poor reproduction. Also I don't think that any of us seriously think that the fragments of chromosomes we observe are Philadelphia chromosomes, because the diagnostic parameter of leukemia is absent. So, it is apparently a fragmentation phenomenon, and not the formation of the specific Philadelphia chromosome. The problem is the general association of chromosomal breakage with neoplasia and leukemia. This is a question, which, as Dr. Hirschhorn has

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[43] Cohen, see footnote 34, page 34.

[44] Irwin, S., and Egozcue, J. Chromosomal abnormalities in leukocytes from LSD-25 users. *Science*, 157:313–314, July 21, 1967.

[45] *Ibid.*

[46] *Ibid.*

## Table 16.—PATIENTS

Frequencies of Structural Rearrangement of Chromosomes (Rearrangements/Cells Involved)

| CASE | Dose 1 | | | Dose 2 | | | Dose 3 | | | Follow-up | | Cells studied | Total rearrangements % after LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pre | 1 hr. post | other post | pre | 1 hr. post | other post | pre | 1 hr. post | other post | | | | |
| A<br>522H | — | — | 10 days<br>1/1*<br>(50) | 1/1<br>(50) | 6/5<br>(50) | 24 hr.<br>7/4<br>(50) | — | — | — | 26 days<br>6/5<br>(50) | 75 days<br>2/2<br>(50) | 300 | 23/300=7.7% |
| B<br>523H | 1/1<br>[2%]<br>(50) | 4/3<br>(50) | 24 hr.<br>1/1<br>(50) | 5/4<br>(50) | 0<br>(50) | 48 hr.<br>2/1<br>(50) | 6/5<br>(50) | 4/3<br>(50) | 48 hr.<br>2/2<br>(50) | 28 days<br>0<br>(50) | 3 mos.<br>2/2*<br>(50) | 550 | 26/500=5.2% |
| C<br>528H | 2/2<br>[2%]<br>(100) | 2/2<br>(50) | 24 hr.<br>0<br>(25) | 4/3<br>(50) | 3/3*<br>(50) | 24 hr.<br>1/1<br>(50) | 2/2<br>(50) | 1/1<br>(50) | 24 hr.<br>0<br>(50) | 2 mos.<br>0<br>(50) | | 525 | 13/425=3.1% |
| E<br>550H | 2/2<br>[4%]<br>(50) | 0<br>(50) | 24 hr.<br>3/3<br>(50) | 0<br>(50) | 5/3<br>(50) | 24 hr.<br>1/1<br>(50) | 0<br>(50) | 1/1<br>(50) | 24 hr.<br>0*<br>(100) | | | 500 | 10/450=2.2% |
| | | | | | | | | | | | | 1875 | |

Numbers in parentheses are total number of metaphases studied per sample.
* 48 hour and 72 hour intervals in culture; all others 72 hour.
All samples taken between 4/3/67 and 8/26/67.

## Table 17.—PATIENTS

### Frequencies of Total Chromosome Aberrations/Cells Involved

| CASE | Dose 1 | | | Dose 2 | | | Dose 3 | | | Follow-up | | Cells studied | Total aberrant cells after LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pre | 1 hr. post | other post | pre | 1 hr. post | other post | pre | 1 hr. post | other post | | | | |
| A<br>522H | — | — | 10 days<br>3/3*<br>(50) | 9/9<br>(50) | 19/14<br>(50) | 10/7<br>(50) | — | — | — | 26 days<br>12/10<br>(50) | 75 days<br>2/2<br>(50) | 300 | 45/300 = 15% |
| B<br>523H | 4/4<br>[8%]<br>(50) | 7/6<br>(50) | 24 hrs.<br>3/3<br>(50) | 8/6<br>(50) | 3/3<br>(50) | 48 hrs.<br>3/3<br>(50) | 13/12<br>(50) | 13/8<br>(50) | 48 hrs.<br>9/9<br>(50) | 28 days<br>0<br>(50) | 3 mos.<br>5/5*<br>(50) | 550 | 54/500 = 9.3% |
| C<br>528H | 8/8<br>[8%]<br>(100) | 4/4<br>(50) | 24 hrs.<br>3/2<br>(25) | 8/6<br>(50) | 4/4*<br>(50) | 24 hrs.<br>7/7<br>(50) | 7/7<br>(50) | 5/4<br>(50) | 24 hrs.<br>2/1<br>(50) | 2 mos.<br>2/2<br>(50) | | 525 | 37/425 = 8.7% |
| E<br>550H | 5/5<br>[10%]<br>(50) | 4/3<br>(50) | 24 hrs.<br>8/6<br>(50) | 3/3<br>(50) | 7/5<br>(50) | 24 hrs.<br>3/3<br>(50) | 4/4<br>(50) | 6/5<br>(50) | 24 hrs.<br>8/8*<br>(100) | | | 500 | 37/450 = 8.2% |
| | | | | | | | | | | | | 1875 | |

Numbers in parentheses are total number of metaphases studied per sample.
*48 hour and 72 hour intervals in culture; all others 72 hour.
All samples taken between 4/3/67 and 8/26/67.

already pointed out, is going to take a lot of time and epidemiological study to clarify.

Now, going back to your data for a minute, I'd like to ask several questions concerning the patients themselves. I'm sorry to say I didn't entirely follow Dr. Shagass' presentation this morning about how he obtained these patients and if they had any LSD before he started treating them.

**Dr. Hungerford:** They had not.

**Dr. Cohen:** If I interpreted your Table 16 correctly, in the pre-LSD sample that you got, there was one cell with a rearrangement. What do these rearrangements mean? Are these quadriradials?

**Dr. Hungerford:** No, by "'structural rearrangement" is meant, in Table 16, all abnormalities except gaps. In the pre-LSD samples from patients B and E, only breaks were present. In the pre-LSD sample from patient C, there was one break and one acentric fragment. The various other types of rearrangement did not appear in the patients until after therapy had begun. No statement can be made concerning patient A prior to therapy.

**Dr. Cohen:** You did not get a pre-dose sample?

**Dr. Hungerford:** Patient A had started treatment a week before we started this study.

**Dr. Cohen:** Well, I think really then that the important point in the entire discussion is the comparison between rearrangement types. You do show an increase in the LSD-treated individuals, and from my own personal experience I don't see chromosomal rearrangements in untreated cells. Were these individuals on anything else before coming in for the study?

**Dr. Shagass:** No, these happen to be more or less drug-free patients. Now, Dr. Hungerford didn't mention that we have a table, Table 18, on the hippies who were on everything under the sun. These are small samples for hippies, 50 cells per hippie. It has been commented that this is a very small sample in Table 18, for the hippie population in Philadelphia, and that you are running three or four of them over 10 percent. You should note that the one who had the highest drug consumption also had the *lowest* percentage of chromosomal breaks.

In your *in vitro* studies, did you use blood samples from hippies?

Table 18.—HIPPIES

Frequencies of Structural Rearrangement of Chromosomes/Cells Involved; and Total Chromosome Aberrations/Cells Involved

| Case | 72 Hr. Cultures | Aberrant Cells | Claimed Drug History |
|---|---|---|---|
| S.E.<br>533H<br>♂ | 6/2/67<br>0; 7/6<br>(50) | $\frac{6}{50}$ = 12% | 16 trips<br>+ other hallucinogens |
| D.S.<br>534H<br>♀ | 6/2/67<br>0; 6/5<br>(50) | $\frac{5}{50}$ = 10% | 20 trips<br>+ other hallucinogens |
| M.A.<br>535H<br>♂ | 6/2/67<br>0; 7/7<br>(50) | $\frac{7}{50}$ = 14% | 9 trips<br>+ marijuana |
| N.S.<br>536H<br>♂ | 6/2/67<br>1/1; 2/1<br>(50) | $\frac{1}{50}$ = 2% | 100 trips<br>+ other hallucinogens<br>+ some hard narcotics |

Numbers in parentheses are total number of metaphases studied per sample.

**Dr. Cohen:** No, these included two technicians, secretaries, and myself; we used pure Sandoz material. I don't think there is any question here about the *in vitro* findings.

**Dr. Shagass:** Of course my interest in seeing what happens was in regard to whether or not I should go on giving people LSD and breaking up their chromosomes. Now for the data that we have in the *in vivo* study—we know what the blood was like before and what it was like afterwards. The results suggest that not much is happening. The fact that *in vitro* and *in vivo* data are very different sometimes is borne out by this discussion. I think that the major issue in this situation concerns the *in vivo* findings. I was interested in the data presented by Dr. Cohen, which suggest that we really ought to stop giving people chlorpromazine. According to these data chlorpromazine seems to be just as dangerous as LSD.

**Dr. Hungerford:** I just want to talk about leukemia once more. I wasn't taking issue with Drs. Hirschhorn and Cohen about the relationship of their data,[47] and Fanconi's syndrome data to leukemia, but simply about this one observation of Egozcue [48] and the subsequent play in the press.

**Dr. Meyer:** I'd like Dr. Warkany to tell us about his work at this point.

**Dr. Josef Warkany:** We've been interested for a number of years in the effect of various teratogens upon chromosomes in the embryo. Conversely, we've also been interested in possible teratogenic effects of substances known to bring about chromosomal changes. Thus, when Cohen, et al.[49] found in 1963 that streptonigrin causes much chromosomal breakage and rearrangement in cultured human leukocytes, we thought that this drug could be helpful in our studies of chromosomal aberrations and teratogenesis. We found indeed [50] that many interesting and unusual congenital malformations can be produced in rats with streptonigrin. It's understandable, therefore, that we became interested in LSD when Cohen and co-workers announced in 1967 that this drug was producing chromosomal abnormalities.[51]

We applied to the National Institute of Mental Health and obtained Delysid (Sandoz/batch 65002) ampules containing 0.1 milligrams LSD per milliliter. A pilot experiment was begun injecting various amounts of the solution intraperitoneally or administering it orally during periods of organogenesis. Single doses were given on the seventh, eighth, or ninth day of gestation, or multiple doses from the seventh to the twelfth day. Total dosage to individual rats ranged from 1.5 to 300 micrograms. Fifty-five pregnant rats were treated. Four litters were completely resorbed; 47 rats were sacrificed on the 21st day of pregnancy and their young were removed; four rats were allowed to deliver and raise their young.

The mean litter size of the 21-day fetuses and the mean weight of the fetuses were not significantly different from those of control animals. We obtained 508 fetuses, and of these, 504 were found to be normal on external inspection; 409 were dissected and 95 cleared for skeletal examination and no abnormalities were found. Only four fetuses were considered abnormal; one had hydrocephalus, one had short extremities and syndactylism, and two fetuses were small. These fetuses appeared in litters which were otherwise normal. No dose dependence could be recognized, and there was no common pattern in the abnormalities of the four young. The four treated rats that we let deliver had 44 apparently normal young, some of which could be raised and bred. No abnormalities could be demonstrated, as they developed and there was no tendency to disease or early death. Since an incidence of about one percent of congenital malformations in the offspring of untreated Wistar rats is not unusual, our pilot experiment did not prove that LSD is teratogenic in rats. Even a dosage as great as 300 micrograms given to pregnant rats did no harm to the embryos. Such dosage is comparable to human dosage. On a weight basis it is more than 200 times larger.

After these experiments were finished we learned of the results of Alexander, et al.[52] who gave single injections of LSD to rats early in pregnancy (fourth day of gestation) and observed resorption of one litter and some stillborn stunted young in others. On the fourth or fifth day of pregnancy we gave 34 rats doses ranging from 1 to 100 micrograms of LSD and obtained from 32 females a total of 335 young. Of these, 296 were removed on the 21st day by Caesarean section. With the exception of one fetus that was small, all were normal on external inspection, dissection, or clearing. Thirty-nine young were delivered and raised. They remain alive and healthy. Two of the 34 rats had no litters A resorption rate of 5.9 percent is not different from that for pregnant Wistar rats injected with saline solution.

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[47] Cohen, see footnote 34, page 34.

[48] Irwin, see footnote 44, page 43.

[49] Cohen, M.M.; Shaw, M.W.; and Craig, A.P. Effects of streptonigrin on cultured human leukocytes. *Proceedings of the National Academy of Sciences,* 50:16–24, July 1963.

[50] Warkany, J., and Takacs, E. Congenital malformations in rats from streptonigrin. *Archives of Pathology,* 79:65–79, January 1965.

[51] Cohen, see footnote 2, page 1.

[52] Alexander, see footnote 36, page 40.

Although most of the doses administered in these experiments were very large (the highest single doses administered by us were about 80 times larger than those given by Alexander, et al.), we found no abnormalities other than reduction in size of one of the young. There were some differences between the experiments of Alexander and ours. They used a dry LSD dissolved in saline while we administered Delysid. We were puzzled by the animals used by Alexander, et al. since they mentioned that their control offspring weighed an average of 64 grams at 10 days. We could not find such rats. In our laboratory, rats weigh about 19 grams at 10 days. Donaldson [53] cites weights of 15 grams for 10-day-old rats. If the LSD-treated rats of Alexander, et al. weighed 44 to 46 grams at 10 days, it would appear that these treated rats weighed more than twice as much as rats in other laboratories weigh at that age.

Thus, we didn't find LSD teratogenic during the organogenetic period, and we found no abnormalities in the offspring of rats injected on the fourth or fifth day of pregnancy although the doses administered to some of the pregnant rats were as high as those used by human beings. We draw no conclusions from the negative results with rats concerning teratogenicity of LSD in man since it is known that a drug teratogenic in one species may not be so in another. This general rule applies also to results in mice [54] and hamsters.[55]

QUESTION: When you repeated this study, what day did you inject on?

**Dr. Warkany:** We did it on the fourth and fifth days.

**Dr. Meyer:** I'd like to go on to Dr. Lisco, Dr. Miller and Dr. DiPaolo before we proceed to a general discussion.

**Dr. Hermann Lisco:** Stimulated by the interesting observations of Cohen, et al. on the effects of LSD–25 on human chromosomes *in vitro*,[56] and encouraged by a number of highly motivated young volunteers anxious to donate their blood, we embarked during the summer of 1967 on studies of chromosome aberrations produced *in vivo* by LSD and psilocybin. This investigation was made in the course of a larger study that has been under way in our laboratory for several years on chromosome aberrations in blood lymphocytes in a number of human populations exposed to ionizing radiations, such as the Marshall Islanders exposed to fallout radiation [57] and others. We were persuaded to look into the possibility of LSD-induced chromosome damage primarily for the purpose of making comparisons of types of chromosome aberrations seen with these drugs and radiations.

Let me briefly summarize our observations to date. They were made on three individuals who had taken LSD only, on four others who had taken LSD in combination with psilocybin, and on four persons who had been given psilocybin in the course of an "experiment" under controlled conditions. Control data were used from normal subjects examined in some of the other studies referred to above.

Cultures of blood lymphocytes were made by conventional methods. Whenever possible, cells were fixed after 48 to 51 hours in culture, since with radiation-induced chromosome aberrations it has been demonstrated that there is a reduction in the yield of chromosome-type aberrations with increasing culture time from 48 to 72 hours and longer. In most cases 200 cells were scored as follows: (a) aneuploid, (b) chromosome aberrations, and (c) chromatid aberrations. Karyotypes were made of most of the cells with chromosome-type aberrations and of cells with equivocal chromosome morphology.

Before describing separately our findings on the three groups of people, some comments must be made on certain features common to all of them. In almost all cultures here studied we have observed stickiness of chromosomes in many cells. This stickiness frequently led to the formation of dicentric-like configurations. These dicentrics were composed of two otherwise intact chromosomes that were firmly attached to each other in an end-to-end association. The terminal portions of the chromatids were perfectly in line with each other, but frequently a small overlap could be seen. Such chromosomes appeared to be firmly joined. On cursory examination many of these structures appeared like *bona fide* dicentrics as seen in radiation-induced chromosome aberrations, but on close examination it was evident that no chromosome material was lost, and there were no accompanying fragments.

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[53] Donaldson, H.H. The rat: data and reference tables for the albino rat and the Norway rat. *Memoirs of the Wistar Institute of Anatomy and Biology, No. 6.* Philadelphia: Wistar Institute, 1924.

[54] Auerbach, see footnote 37, page 40.

[55] Geber, see footnote 38, page 40.

[56] Cohen, see footnote 2, page 1.

[57] Lisco, H., and Conard, R.A. Chromosome studies on Marshall Islanders exposed to fallout radiation. *Science,* 157:445–447, July 28, 1967.

These structures have been scored and classified as a special category of dicentrics, and they are included in the overall aberration rates. It should be mentioned that such dicentric chromosomes are occasionally seen in controls, but we have no estimate of their rate of occurrence at present. However, they have been observed in the present material with such frequency that they must be included in the estimate of aberrations. Another feature worth mentioning is the fact that translocations and inversions have not been observed in excess of what would have been expected in the 3,189 cells scored in this population as compared with a similar number of cells in the controls. One was found in each group.

Two young men who had taken a total of 980 micrograms and 480 micrograms of LSD respectively in several small doses for about a year and one-half prior to examination showed nothing unusual, with the exception of a single dicentric of the sticky type in 200 cells in one of the men. Chromatid breaks were within normal limits with 2.5 and 6 percent respectively. Several months later the previously aberration-negative person and a companion took a single dose of about 500 micrograms of LSD; they experienced marked psychic effects lasting several hours. Examination of both individuals five days later showed an incidence of 16.5 and 25 percent chromatid breaks, increased numbers of acentric fragments, and also a few dicentrics of the sticky type in each. Reexamination of one of the individuals 16 days and three months later showed a decrease both in chromatid breaks and in chromosome aberrations but not a return to normal.

The four persons who had ingested both LSD and psilocybin in varying doses from 10 to 36 months prior to examination also showed increased rates of chromosome aberrations but no excess numbers of chromatid breaks. There were increased numbers of dicentrics of the sticky type as well as of the classic type, some of them with fragments; one individual showed ring chromosomes.

The four individuals who had taken a single dose of psilocybin (40 and 30 mg) from 18 to 20 months prior to examination also showed increased rates of aberrations, including both types of dicentrics and of rings. Chromatid aberrations were within normal limits. To our knowledge these four individuals had taken no other hallucinogenic drugs either before or after the ingestion of psilocybin.

The results from this limited number of individuals support the observations of Cohen and of others since then that LSD can produce chromosome damage in human lymphocytes. Furthermore, they provide evidence that another hallucinogenic drug, psilocybin, has similar effects and that these effects can persist for 20 months and probably longer after a single dose of 40 mg. Lastly, these observations indicate that the mechanisms of production of chromosome aberrations by these drugs may be different in some important respects from those involved in radiation-induced chromosome damage.

**Dr. Meyer:** Could we move on to the last two speakers? Dr. Miller.

**Dr. Robert Miller:** I'm Dr. Robert Miller of the National Cancer Institute. As an epidemiologist, the rare breed to which Dr. Hirschhorn has alluded, I would like to talk at length, but will not. I'll hardly talk at all. I would like to reserve the time during which I would have spoken for some discussion as to important roles that the NIMH can play in exploring some of the questions raised at this meeting. I would suggest, however, that epidemiology plays a very large role. Almost every presentation this morning and this afternoon either concerned an epidemiological study or had implications for them.

**Dr. Joseph DiPaolo:** I wish to make reference to the carcinogenic, teratogenic, and blood studies which have been in the literature for some time. In addition, I should like to add comments concerning some of our own results.

In 1959, Berenblum, et al.[58] reported that although LSD was a powerful antagonist against the anesthetic effects of urethan, it was ineffective in eliciting any antagonism against the carcinogenic action on the lung or against the initiating phase of skin carcinogenesis induced by urethan in mice. A single injection of LSD failed to potentiate or minimize the effect of urethan.

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[58] Berenblum, I.; Blum, B.; and Trainin, N. Failure of the urethan antagonist—Lysergic Acid Diethylamide (LSD-25)—to inhibit lung carcinogenesis or the initiating phase of skin carcinogenesis in mice. *Biochemical Pharmacology*, 2:197–199, September 1959.

In reference to teratology studies, I should like to point out that there has been a recent paper in *Science* by Dr. Auerbach.[59] This work appears to have been well carried out. The frequency of malformations is high but it should also be taken into consideration that the controls have 10 percent abnormalities. In all cases the malformations involved brain defects. It would be nice to see this work expanded, particularly since it had been reported by Auerbach that one dose level of LSD appeared to be ineffective. I have commented at length on the rat studies which were reported by Alexander and I understand that these comments will appear as a technical note in *Science*.[60] Our own attempts to demonstrate teratogenic response with LSD have involved two strains of mice and one strain of hamsters. In no instance were we able to demonstrate that LSD produced malformations. The amount of LSD we used varied by astronomical figures from that reported to be successful by Auerbach.

The next reference I wish to point out is a paper by Sackler, et al.[61] which showed the effects of acute and prolonged administration of LSD on white blood-cell count, body weight, and organ weight. "Tail blood samples were taken immediately prior to autopsy. Marked or significant decreases were noted in total white blood cell counts as well as lymphocyte and eosinophil frequencies. Food consumption was affected more adversely during the first week. Analyses of the absolute organ-weight data revealed significant reductions in the thymus weights of both test groups, with consistent but smaller decreases in the thyroid and uterine weights of the test animals. Although administration of LSD to female Wistar rats demonstrated greater resistance and less pronounced effects than those noted in males, the results still indicated stimulated adrenal activity with suggestions of hypothyroidism and hypogonadal function." Because of this effect on white count, in particular lymphocytes, I think it would be interesting and desirable to attempt to culture other types of cells in the presence of LSD or to take biopsies or any fluid such as amniotic fluid which has been in an LSD environment. There are techniques such as the cellophane method which may be utilized for small biopsy specimens. With practice it should be possible to obtain cellular immigration within a few days after cultures are set. These then could be analyzed for chromosomal anomalies. In addition, embryonic and/or fetal tissue from a variety of sources should be exposed to LSD.

**Dr. Meyer:** Thank you. I would like to focus our discussion now on comments, namely, initiatives that the Institute can take and the role of epidemiological studies in defining the problems raised here today.

**Dr. Freedman:** There are several people here who were given LSD in the 1950's, and it may be possible to ascertain the state of their chromosomes. I would recommend that Dr. Miller, who has great experience in doing such studies all over the country, could get in touch with the people here or others whom he may know and let us find out the status of their leukocytes and their offspring.

**Dr. Smith:** I'm in full agreement that epidemiological studies are necessary, but I think that the gentlemen here have to realize what has happened relative to the drug-using population. Certainly if we did demonstrate that chromosomal abnormalities were produced by LSD and that they did have teratologic effects, then at that moment in time the issue would still not be settled for the drug-using population. Our community of several thousand people who consistently use LSD from one time per month to two times per week have been widely refuting the initial reports about LSD and chromosomes. In fact there have been a series of recent articles published in the underground press; one under the esoteric title, "Acid Burned a Hole in My Genes," openly stated that the data that has been presented was a Government-sponsored plot to stamp out the use of LSD. I think we've got to realize that we can get a great amount of epidemiological data, but the credibility gap is so wide that we also ought to address ourselves to putting this data in a form that the drug-using population will believe. If we prove that there is chromosomal abnormality secondary to LSD usage, then the only way to prevent it is to have the individual stop taking LSD. If the user believes that your data is epidemiologically false and that it's designed specifically to induce him to stop taking LSD (as is the current and dominant attitude now in Haight-Asbury), then the Institute should address itself not only to epidemiological studies but also to techniques of education that the drug-using population will believe.

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[59] Auerbach, see footnote 37, page 40.

[60] DiPaolo, J.A. LSD: effects on offspring. *Science*, 158:522. October 27, 1967.

[61] Sackler, A.M.; Weltman, A.S.; and Owens, H. Endocrine and metabolic effects of Lysergic Acid Diethylamide on female rats. *Toxicology and Applied Pharmacology*, 9:324–330, 1966.

**Dr. Hirschhorn:** First of all, there seems to be a difference in attitudes between the East Coast and West Coast. The *East Village Other* had a very favorable article regarding the potential dangers of chromosomal damage. It was recently determined that a great number of individuals in the New York area have in fact gone off the drug on the basis of this article. I think however that publication [illegible] is insufficient. The type of contact that Dr. [illegible]h can have and that some of us have had directly with these people, in which we do not tell them "it's going to cause damage," but simply describe the possibilities, is extremely effective.

**Dr. Meyer:** Apropos of that in terms of the epidemiological studies, there are two questions we have to be concerned about. First, if in fact these drugs do have long-term effects, this would raise serious questions in terms of the research efforts with the drugs; the second issue is that there is a credibility gap not only between the Haight-Asbury and the professional community but within the professional community itself. I think we've uncovered here a degree of disagreement among various competent research people as to what these findings really mean. I also think that we do have a position that we must uphold, which is to find out what these things mean. I think we can only find out through epidemiologic and other research. I see some other hands up so I'd like to pass the microphone to Dr. McGlothlin, and then to Drs. Levine, Osmond, and Robert Miller.

**Dr. William McGlothlin:** I just wanted to mention briefly a study that we are carrying out now, which is a follow-up on 300 persons who took LSD six to ten years ago through a physician who did an experiment in therapy. It looks as though about a third have continued to take LSD to some extent. We are looking at birth defects and miscarriages, etc. If any of you have some ideas of other things that we should be looking at, I'd appreciate it if you'd contact me.

**Dr. Levine:** With all due respect to epidemiological studies it might be a lot less expensive to do a really controlled study of whether the drug results in chromosome breaks. In looking at the results here, one wonders how one finds controls for so-called hippies. In other words, how does one find controls for people who live a very peculiar kind of existence in which a great deal of abuse of the organism goes on aside from LSD? I think one can't be convinced by these kinds of controls. The one study in which there is a pre- and post- kind of thing is much too small to draw any conclusions; two of the four patients actually go down in regard to chromosome problems and two go up. I don't think there's any hard evidence with regard to chromosome breakage in humans from the data that we've seen today.

**Dr. Osmond:** Just two points. We see quite a lot of agreement that LSD could be usefully and safely given to people whose perceptions have become stabilized and who are probably beyond their reproductive life. This seems to be rather surprising. The other point is that I would strongly agree with Dr. Smith that what is needed with this information is a "soft-sell"; the attempt of battering at the hippies and others for about five years with a club has simply produced obstinacy. They are not sure that the drug is very good for them; perhaps if we change our ground here, it gradually will seep into them that there are dangers, and they will think about these and then gradually change. If, however, we try to bulldoze our way through, we'll run into all those qualities that we actually admire in people whose views are being attacked.

**Dr. R. Miller:** I too think that epidemiology isn't going to be the answer by itself. There has to be a close interaction between laboratory, clinical, and epidemiological observations, but the final application to man of concepts developed at the bedside or in the laboratory will be determined by epidemiologic study. We're not afraid to report studies which are negative. We do it all the time. And such negative findings should be reassuring to persons who want to use these drugs for therapeutic purposes.

**Dr. Wynne:** I'd like to raise for further study and consideration the problem that was suggested in some of the data about other drugs such as chlorpromazine which seem to have similar effects. That kind of finding would pose problems, I think, for epidemiological studies where you have people who have a great variety of life experiences with drugs, with therapeutic and diagnostic X-rays, with malnutrition, with virus infections, etc. I'm greatly concerned, therefore, that if these studies are going to be definitive, the problems of adequate controls must be very carefully scrutinized. I think this is of the utmost importance.

COMMENT: I'm going back to the question of the effects of publicity, whether it is good or bad. It was mentioned that it may be good because it will scare a few or perhaps many young people from taking LSD. There is a reverse side. There are many pregnant girls now who have taken LSD, and you know what it can do to a pregnant woman to be told that she has to expect an abnormal child. Secondly, I think there may be abortions being done right now because some women have taken LSD.

**Dr. Hirschhorn:** As I understand it, none of the data on subjects receiving chlorpromazine showed rearrangements. These were chromatid and isochromatid breaks and not rearrangments. The other issue is that these people were currently receiving chlorpromazine and had blood levels of chlorpromazine. It has not yet been determined whether this is a long-lasting effect; we're doing a study to see if it is. These were the features which distinguished the LSD subjects from the chlorpromazine subjects.

**Dr. Shagass:** In response to your comments, we do have an enormous number of people in whom we deliberately maintain a high chlorpromazine level, and we get very worried when it isn't maintained, because they relapse into a psychosis.

I'd like to address a question to the chairman regarding what sort of postural issues he wants to discuss. It seems to me that we've got a number of things here. The most important one, however, is that an otherwise small, yet important (but not sensational) scientific finding about the chromosomes was precipitated into a furor by virtue of publicity in a climate of concern. Certainly, as far as my own investigations are concerned, I am hit negatively because my subjects are not hippies; they are not people who are drug users, but they are very frightened about being treated with LSD, and I have to reassure them. My motive in getting Dr. Hungerford to do this work was to know whether I had a basis for reassurance; surely the data are small but, so far, I haven't seen anything that convinces me that I don't have a basis for reassurance of a mild degree.

**Dr. Meyer:** I think that what we're aiming for here is a definition of some of the questions. Perhaps it is the Utopian fantasy of a Government scientist sitting in this building which makes me feel that getting people together of the competence that's in this room will clarify questions (if not provide answers). Additionally the Center is interested in supporting research and getting people of different research competencies together, specifically the way you and Dr. Hungerford have done in Philadelphia. These are the kinds of observations that need to be made, and I think that only by finding out some of the data that are available, as we have today, can we begin to look more systematically at the problem. We're looking at it from several different levels; when the meeting started this morning it appeared almost as though the people who were giving LSD for treatment would be on one side and the people who observed adverse reactions would be on the other side. I think what's emerging is that we have many levels of observation and that they aren't contradictory; rather, I think that they are complementary.

**Dr. Freedman:** I think there's only one posture that you can take and that is that you're in a Bureau now, but that you came from traditional institutes which fostered research. You should invite research; make it clear that you'll receive research proposals and that you'll program research. You're in danger if you program *all* the research from here by contract. I think there's some that you can do best. The question of posture is governed by somebody who controls the budget; you have to have enough funds to disperse to extramural scientists for those studies considered by you and your advisors to be useful and important.

**Dr. Silverman:** I'm not sure of just how to go about this, but it ought to be possible to develop a safe atmosphere within which hippie types could take *their own* drugs under NIMH supervision. The aim of such a project would be to get a line on the contaminants in LSD which are being used in its manufacture in the various areas of the country. At present there is no way of getting people into our laboratories to study them while they are on their own drugs.

**Dr. Joffe:** I think we've got to facilitate information exchange. We can get the material for you; you get the volunteers.

**Dr. Shagass:** I just wanted to say something about this problem of communication. I got these four blood samples from hippies by simply saying to our student health psychiatrist that I would like to get some and he said, "Well, will you pay them?" and I said, "No, just tell them that I'll let them know if they have any chromosomal abnormalities." I got a call the next day and he offered me ten subjects, and he asked how many I wanted. I don't think that's an attitude of massive denial. These kids are running scared. I think that what's been reported is not inconsistent with that, but our responsibility is not to feed them scare information, but information.

**Dr. R. Miller:** I would like to suggest that a role for NIMH is to try to identify gaps in our knowledge to be filled either through direct research by NIMH, through contract research, or grants; NIMH, perhaps, would want to reserve for itself studies which cannot be done so effectively by other organizations, such as universities or drug companies.

**Dr. Hungerford:** I just wanted to ask one question. It seems to me that one of the experiments that needs to be done is to administer illicit LSD to hitherto unexposed patients, but I wonder how many physicians would consider this to be ethical? You can't do it *in vitro* because as we've learned today Sandoz LSD has essentially the same effect *in vitro* that illicit LSD has. Work with primates might not be entirely relevant, because monkeys aren't people either. There might be human volunteers from various sources, conscientious objectors and prisoner populations, for example.

**Dr. Joffe:** I think perhaps with a little more digging we would have the model system that biology could present to study this particular group of drugs and we may be able to utilize an animal model.

COMMENT: I'm neither an epidemiologist nor a geneticist but I was intrigued today by the finding that it looked as though the highest rate of abnormalities in these cells was noted in two control patients who were dismissed as being unimportant because two days later they came down with a viral infection. It seems to me that viral infections are a lot more prevalent (I guess that's an epidemiological word) and maybe we'd better focus our attention on that.

**Dr. Hirschhorn:** What has to be remembered about the difference between the findings with LSD and radiation as against the findings with viral infections and probably chlorpromazine is that with LSD and radiation the findings are long lasting; the findings contain chromosomal rearrangements. In regard to transient viral infections, the findings occur for a few days and they have been shown not to affect other somatic tissues (which radiation does). The chlorpromazine studies so far do not show rearrangements; the transient viral infections produce simple breaks and not rearrangements, whereas the oncogenic viruses, for example, in tissue culture do cause rearrangements and are long lasting in culture, similar to the *in vivo* studies with radiation and with LSD. There's a world of difference between the kind of finding that you get in someone who has a transient viremia and someone who has had LSD eight months ago. You just can't put the two in the same basket.

QUESTION: How about things like hepatitis?

**Dr. Hirschhorn:** Hepatitis, so far as I'm concerned, has some questionable effects on chromosomes, and again, when they're there, they're very transient.

QUESTION: These findings are all based on a group that's had LSD many times? Are these the results presented by Dr. Cohen?

**Dr. Hirschhorn:** No, we've heard today about permanent and long-term chromosomal aberrations in persons exposed on one occasion to psilocybin in an experiment. It's unrealistic to think that you're going to be able to track down all the contaminants in these kinds of things. You can't get an answer to the question of impure substances.

**Dr. Pahnke:** I'd like to make a practical suggestion. I would say that anyone who's working with LSD at the present time might be encouraged to do some collaborative studies with a geneticist. For instance, at Spring Grove we hope to study a host blood sample to get the sort of thing that Dr. Hungerford has done. I think we need a lot more studies like that.

**Dr. Meyer:** Thank you all very, very much. I think you have done a magnificent job of defining the significant questions and suggesting relevant research strategies. I hope that we can be as successful in implementing these investigations.

# Summary of The Conference

The extent and characteristics of hallucinogenic drug abuse among middle class young adults is at this time unknown. Preliminary reports of grant-supported surveys in the spring of 1967 indicated that 15 to 20 percent of the college population had used marihuana and approximately 6 to 8 percent of this same population had used LSD (and/or other hallucinogenic drugs). Much of this could be characterized as "experimentation." Within hippie gathering places, however, drug use more clearly approximates drug abuse with persons regularly taking multiple and more dangerous compounds.

Some clinical and research observers of the LSD scene have observed a discrete pattern of psychopathologic behavior among chronic users of LSD and persons on "bad" trips. These professionals have been concerned about possible outbreaks of new forms of organic psychosis related to hallucinogenic drug use. Preliminary reports from various biological laboratories have also suggested the possibility that LSD may be implicated in serious chromosomal aberrations. These observations have led some to conclude that LSD may be leukemogenic and/or teratogenic. Concerned with these reports of psychological and biological damage, the Center for Studies of Narcotic and Drug Abuse on September 29, 1967, convened a meeting of leading research investigators in this area. This report summarizes the proceedings of this meeting.

Most participants deplored the complication of reasonable research deliberation by exaggerations in the popular press and the tendency to draw conclusions from preliminary data. Some participants confirmed the spread of intravenous methedrine abuse in some of the hippie communities and described the outbreak of STP use which took place early in the summer of 1967. The original reports which had indicated that chlorpromazine potentiated STP trips in a dangerous manner were specifically refuted by several participants. This drug (STP) was felt to be more typically adrenergic, consistent with its chemical structure.

Evidence of persisting psychological damage from chronic LSD administration was minimal. This negative finding may be "real" or may reflect a lack of sophistication in our measuring instruments. While some psychological tests done on persons who have used LSD many times suggest borderline evidence of organicity, electroencephalographic findings subsequent to LSD administration (but not during the LSD trip) are generally normal. Dr. Julian Silverman, reporting on a study done with eight chronic LSD users at the National Institute of Mental Health, indicated that amplitudes of EEG evoked responses (secondary to photic stimuli) were elevated in some chronic LSD users (while not under LSD). These higher amplitudes paradoxically returned to normal levels when 50 micrograms of LSD was administered. Of some interest was the observation that these chronic users (when not on LSD) showed uniformly lower thresholds to auditory stimuli, and that these thresholds resembled those of Addisonian patients being withdrawn from steroid maintenance. This suggests the possibility that sensory overload may be a problem for some chronic LSD users, even when they are not on the drug. It was speculated that, in some way, this phenomenon may be related to the absence of goal-directed behavior among the chronic users of LSD.

Dr. Humphrey Osmond of the New Jersey Neuropsychiatric Institute and a pioneer in early research efforts with LSD confirmed some of Dr. Silverman's findings by his own observations at the New Jersey Neuropsychiatric Institute.

Other participants focused on the treatment of the "bad" trip. Some noted that chlorpromazine has been ofttimes ineffective and, that in some centers, routine sedation and psychological support is the preferred treatment. Most participants agreed, however, that the psychiatric community should gain increasing familiarity with this new syndrome and that each psychiatrist should develop familiarity with a treatment program that could include phenothiazines and/or the use of sedative drugs and psychological support. Several clinicians present noted that "bad" trips are seen almost exclusively among persons in the 15 to 25-year age group. One postulated that this relationship might represent the potentiation, by LSD, of adolescent adjustment problems into severe acute crises.

Several participants described the phenomenon of recurring psychedelic experience without recurrent ingestion of the drug. Of particular concern were descriptions of recurrent paranoid episodes, at times accompanied by vivid hallucinations, in some users of LSD. There were neither psychological nor pharmacological explanations of this phenomenon, but the LSD experience generates powerful emotions and any affectively rich experience is bound to recur in the mental life of the individual.

Dr. William Frosch, of Bellevue Hospital in New York, reported the continuing admission of two patients per week to the Psychiatric Service secondary to LSD use. Dr. Thomas Ungerleider of UCLA indicated that the large number of LSD admissions to the emergency room at UCLA caused the Psychiatric Service to close its doors to those experiencing "bad" trips. While some have reported that the frequency of "bad" trip admissions to general hospitals and other institutions has been decreasing, it appears that this is still a continuing problem for mental health professionals. Additionally, a number of participants pointed to the phenonenon of depression among chronic users of LSD. This depression has been particularly refractory to traditional psychiatric treatments and the participants were not agreed on the nature or treatment of the phenomenon. Unfortunately, many chronic LSD users have turned to amphetamines in an effort at self-treatment of the depression.

Relative to the question of leukemogenic or teratogenic properties of LSD, Drs. Maimon Cohen and Kurt Hirschhorn summarized their data relative to LSD and *in vivo* and *in vitro* chromosomal aberrations. Since their initial report in *Science* [62] they have also observed chromosomal damage secondary to chlorpromazine and certain other tranquilizing drugs. They noted, however, that these aberrations were not as severe as the dislocations and translocations observed secondary to LSD administration. Dr. David Hungerford of the Cancer Research Institute in Philadelphia also reported investigating the circulating lymphocytes of some hippies in the Philadelphia area but failed to confirm Dr. Cohen's findings. On the other hand, Dr. Hermann Lisco of Harvard University observed similar chromosomal changes in persons who had been given psilocybin in a psychological experiment. Persons attending this meeting were unclear as to the ultimate significance of these findings. Dr. Robert Miller of the Epidemiology Branch, National Cancer Institute, noted that time would be the significant factor in observing the evolution of possible leukemia-type syndromes. Underlying all of the discussion was the concern that these reported chromosomal changes have also been observed in survivors of the Hiroshima attack and other persons exposed to high doses of ionizing radiation, all of whom have an increased likelihood of developing leukemia-type syndromes.

Early reports from Dr. Auerbach [63] at the University of Wisconsin noting teratogenic effects of LSD administered to mice (plus an increase in the rate of spontaneous abortions) were not confirmed in studies done on rats by Dr. Josef Warkany of the Children's Hospital, Cincinnati. Subsequent reports of teratogenic effects in the hamster suggest species differences in fetal response to LSD.

Some reports subsequent to this meeting suggest that the chromosomal changes secondary to LSD may be transient phenomena similar to those observed in viral illness and therefore not analogous to the chromosomal changes observed after radiation exposure (which are permanent). At this time our information about the biological hazards of LSD and other hallucinogenic drugs must be considered incomplete. One observer at the meeting said that he almost wished that some of these reports about chromosomal damage were true so that we could stem the increase in illicit hallucinogenic drug use. But the jury is still out. We would certainly continue to warn potential mothers about the possible hazards of LSD exposure; being always clear about our facts while avoiding scare techniques. The group was unanimous in feeling that scare techniques only alienate the drug-using community so that they may not at some future time listen to scientific facts about confirmed hazards of hallucinogenic drug use.

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[62] Cohen, see footnote 2, page 1.

[63] Auerbach, see footnote 37, page 40.

# APPENDIX

## Background Papers and Bibliography

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# On the Use and Abuse of LSD

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While scientists may debate the appropriate use of hallucinogens, history records our unceasing urge to cope with dreary reality or dread with the aid of magic, drugs, drama, festival rites, and (with biological regularity) through dreams. The need to transcend limits also finds a voice in utopian ideologies—be they of the inner world, of this, or the next; the promise of omnipotent mastery is always either implicit or readily inferred. Thus whether it is the proletarian masses, or youth mesmerized by mellow yellow banana, or the princes of the land of genital primacy, or the meek—each is promiced the inheritance of what probably will be a rather crowded earth. Given the prevalence of these motives it is not surprising that drugs play a role not only in the behavior of individuals but also in social and ideological processes.

With the appropriate motives and occasion, almost any psychoactive drug can provide a brief "ego disruption"—producing a moment of being out of it.[1] This disruption *in itself* may promote the release of powerful affects and this ego state will be welcomed for its novel value as a remarkable trip from reality. Etched upon it may be the specific pattern of the drug. I believe that the action of drugs such as LSD extend and accent this primary ego state in a salient and sustained way. In any event, scrutiny of the social use of drugs cannot infallibly discriminate the "basic" pattern of effects. We first have to distinguish the range of effects of "ego disruption" *and* what is commonly called the power of suggestion. With this in mind, we can focus on the ways in which hallucinogens do and do not selectively enhance suggestion and various psychological and ideological phenomena.

The reported consequences of drugs such as LSD range from isolated awe or benign or even bored surprise to shifts of values. They range from transient to long-term psychoses to a gamut of confusional states and depression to varieties of religious or aesthetic experience and insight, to clique formation and ritual.[2] There are now conflicting reports of therapeutic effectiveness in alcoholism, depression, character disorders, and severe neurosis.[3-12] There is also a mushrooming psychedelic culture. This underlies the tribal motions (or brownian movements) of young and aging dropouts, rebels disavowing society's "games" if not all (nonmusical) instrumental behavior. The paraphernalia of fringe fashions, music, and art comprise the trappings and trippings commercialized as psychedelic "go-go." Some serious theologians, some "hippies" as well as our peripatetic prophets now seek the drugs as a promoter of love, of religious or self-enhancement. Some view the drug as transforming western society into a Zen Elysium. Some are sincere and private in these pursuits, some provocative and evangelistic, and there are variant subgroups whose rapidly evolving habits, ideologies, and behavior are as yet unrecorded.

Of course, gentle and ferocious reformers have often held that special visions were not only their inspiration but their explicit guide. The elite threaten misery for those who do not accurately assess—ie, agree with—their claims of value. Truly dispassionate assessment—the exercise of judgment—may deprive one of access to the mysteries revealed in special states; there is only one way to be "in" on the truth—*their* way—and if one is "in" there may be no way out! The only answer to such dilemmas posed by any cult is exposure to ex-

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perience, to knowledge, and assessment over time—ie, perspective.

### The "Psychedelic" Dimension in Behavior

The recurrent theme in historical records is that certain drugs are compellingly related to "learning," to self-revelation, and that they are involved in some mystical, often ritual, use.[13] The American Indian often states that "peyote teaches." This major theme does not dominate ordinary accounts of marijuana usage. The *potent* preparations of cannabis—charas and ganja—are an exception and have been used in India to enhance contemplative states as well as for a "high" and are not without paranoid and other psychotomimetic effects.[14,15] Apparently, there is a continuum of effects along the dimension of self-revealing and ritual usages.

To the extent that there *are* classes of agents which reveal normally suppressed components of the mind—exposing these dimensions to our attention—we can say that both use and abuse stem from an amazed response to a drug-induced subjective experience. If this is what Humphrey Osmond meant by the term "psychedelic" (or "mind manifesting"), it is an apt though not novel description. Whatever the outcome, the mode of functioning and experiencing called "psychedelic"—or "psychotomimetic"—reflects an innate capacity (like the dream) of which the *waking* human mind is capable.[16] The fact that a certain class of drugs so sharply *compels* this *level* of function (with all the variability inherent in less organized states) and does so for a chemically determined package of time is what so intrigues the biobehavioral scientist.

From our work over the past nine years,[17-19] we now know that the indole and catechol derivatives which are psychotomimetic in man can induce a response in the brain of animals, altering brain serotonin metabolism and probably increasing the utilization of norepinephrine. Most of these drugs show crosstolerance. In contrast, psychotomimetic agents such as atropine or piperidylglycolates (eg, Ditran) which produce amnesia and delirium [20-22] primarily affect brain acetylcholine rather than monoamines.[19] This indicates that we are dealing with agents for which some exquisite molecular [23] and biological specificity exists; each of the brain monoamines appears to be lawfully related to specific, largely polysynaptic neural systems and it is not unlikely that with autoradiography, and fluorescence and electron microscopy,[18,24] our knowledge of the involved neural systems and chemical changes induced by these drugs can be ever more finely specified.

At the behavioral and experiential level this specificity has intrigued many. William James,[25] who had taken mescaline, wrote that there are potential forms of consciousness which with . . . the requisite stimulus and at a touch . . . are there in all their completeness . . . somewhere (they) have their field of application and adaptation . . . How to regard them is the question . . . *they may determine attitudes though they cannot furnish formulas and open a region though they fail to give a map* (Italics mine).

What about the experience of this "region" of the mind is so striking? Two features are obvious, the nature of the experience and the contrast with ordinary experience. It is my impression that one basic dimension of behavior latently operative at *any* level of function and compellingly revealed in LSD states is "portentousness"—the capacity of the mind to see more than it can tell, to experience more than it can explicate, to believe in and be impressed with more than it can rationally justify, to experience boundlessness and "boundaryless" events, from the banal to the profound. If we were to relate this to psychoanalytic theory, we would say that an ego (or cognitive) consequence of the primary process and its hypothesized mobility of energies is this dimension of "portentousness." Affects are equally mobile; fragmentations and fusions—plasticity—are, as Freud described it for dreams, characteristic.

To this disjointed world of clear perceptions one can react with awe rather than tempered judgment, or even with irrational and boundless affect—ecstasy or terror. The *sense* of truth is experienced as compellingly vivid but not the inclination to test the truth of the senses. Unlike the sleeping dreamer, the waking dreamer is confronted with the coexistence of two compelling and contradictory orders of reality—with the interface of belief and the orderly rules of evidence.

James saw this as a region of the mind which knows *both* mysticism and madness; ". . . there seraph and snake abide side by side." But experiences of this realm of the mind cannot be totally disconnected from normal life; how they are connected is the crucial issue. As James remarked, what comes from this inner world must, ". . . eventually run the gauntlet of confrontation with reality just as what comes from the outer world of our senses." The "trip" back to reality after "tuning in" to this region may be discordant or harmonious; one's sense of both the inner and outer world may be revised in the service of the ego or altered to suit the requirements of irrational needs. There are, then, modal and characteristic forms of mental operations which can underlie behavioral states and experiences of widely different consequence, intent, and meaning; and these modal operations are common both to madness and mysticism which must be differentiated on other grounds.[26] To summarize, I believe that there are few drugs which can so unhinge us from the constancies which regulate daily life, or so clearly present us with unevaluated data from the "inside world" and from the many normally useless perceptions potentially available to us. It clearly has been tempting to snatch some good from this. It also can do little harm, given such an ample smorgasbord of claims, to seek perspective by concentrating on what—if anything—is common to all of these varied effects of LSD.

What must be described is a multipotential state which, in its most general sense, can underwrite a variety of outcomes: religious feeling and conversions, states of hyperperception leading to inspirational insights, to psychosis, to exalted states, or perhaps to behavior or value change. The more we can grasp some of the intrinsic features of this state, the more we will be able to predict and understand why such drugs can be properly called psychotomimetic, psychedelic, or "cultogenic" agents. It will also be clear that some of the modes of experience—the *styles*—which characterize the drug experience can be linked to the outcome or to the style of life commonly centered around drug taking: whether this frequently persistent "hangover" of drug effects represents new learning, or reinforcement of the ongoing trend of goals and adaptations, or more complex mechanisms is not now known. Beyond impressions which are hardly sanguine about long-term use, evaluated data are still lacking.

## Pharmacological Features

The sequence of effects following the usual doses has been described elsewhere.[27] During the first 4½ hours there is generally a clear-cut self-recognition of effects—an internal "TV show" (marked by shifts of bodily sensations, affect, and perception) which is followed by another four- or five-hour period in which the subjective sense of change is less marked but during which heightened self-centeredness, ideas of reference, and a certain "apartness" are observed. At 12 to 24 hours after drug there may or may not be some letdown and slight fatigue. There is no craving to relieve this and no true physiological withdrawal.

Contrary to previous myth, the acute stage correlates with the biological half-life of the drug in plasma in rat[28] or man[29]; and the duration of what can be identified clearly as drug related effects is dose dependent, lasting generally 8 to 12 hours. There is a dose-contingent tolerance in both rat and man requiring three or four daily doses for maximum effect and about four days for a loss of tolerance[30]; with high dosage there is an unexplained cyclicity of tolerance—a sudden loss after eight days and then a gradual build-up with continued dosage.[31] With doses of 200 to 1,000$\gamma$ there is, with increasing dosage, an increasing loss of autonomy and control of critical and discriminative functions. Usually, one "trip" produces "psychological satiation"[13] and is sufficient for most people forever and for others, at least for a few days, months, or years.

## The Drug Experience

It is the intense experience without clouded consciousness—the heightened "spectator ego" witnessing the excitement, which is characteristic for these drugs in usual dosages. Thus there is a split of the self—a portion of which is a relatively passive monitor rather than an active, focusing, and initiating force, and a portion of which "receives" vivid experiences. Some people seem to repeat this long after the drug state; standing apart from life and its "games" or relying on the group to direct events, they turn away from the prosaic world—or else are turned away by society. The striking self-centeredness—the experience of the self seeing the self—can be elaborated in a variety of ways, from detachment to symptomatic narcissism. The dominant experience of seeing can be expressed as convictions of revelation—ie, psychological, mystical, aesthetic, or religious "insights."

During the drug state, awareness becomes intensely vivid while self-control over input is diminished, fragile, and variably impaired. Thus there is always the lurking threat of loss of inner control—loss of control of integral stability. This is variably experienced and symbolized. At its height, it has been called "dying of the ego" and is often reported in bad trips or in phases of mystical experiences with the drug. For some, such experience is dread transcended; for others, it is unwelcome or denied anxiety and dyscontrol. Many anxious concerns and problems after the drug state center around issues of control, autonomy, self-directedness, and decision making.

In the drug state, customary boundaries become fluid and the familiar becomes novel and portentous. Any event or category of events which comes to one's attention—sensory, sexual, or cognitive—takes on a trajectory of its own. Qualities become intense and gain a life of their own; redness is more interesting than the object which is red, meaningfulness more important than what is specifically meant. Connotations balloon into cosmic allusiveness. This can be experienced religiously, aesthetically, sensually, or in a variety of clear or confused frames of reference.

After the drug state, we may find pseudoprofundity[2,32] or omniscience as well as more tolerance for the novel, the unusual, or for ambiguity. We also can find an associated inability to decide, to discriminate, to make commitments. This occurred as a Rorschach pattern in Indian peyote users.[33] Such a tendency to avoid distinctions could lead to alienation and retreatism, even if these were not preexisting traits (as they often are). For many, the drug experience may represent a beginning—an attempt to feel intensely—which without luck or expertise, cannot easily come to a useful conclusion (just as neurotic acts may be viewed as unguided attempts at self-cure).

Certainly when hidden meanings perpetually contaminate the response to the explicit conventions of everyday life, "focus" and goal-directed efficiency are impaired. Judgment is not enhanced during the drug state and isolation or apartness bring their own problems: accordingly persons who continually overvalue the modes experience of the drug state could develop and reinforce poor practical habits. Pseudoprofundity, philosophical naivete, impractical detachment, and inadequate foresight and judgment or impulsiveness in dedicated users were already evident to an observer of the Harvard scene of 1963.[32] The consequences of long-term and frequent use of the drug—involving possibly 5% to 15% of those experimenting with LSD—would probably have to be evaluated in this context.

## Immediacy, Novelty, and Creativity With LSD

In the drug stage, the experience of compelling immediacy diminishes the normal importance of past and future. One's organized anticipations of time dissolve and the anticipatory factor, so important in the psychophysiology of pain, is similarly affected. (This—coupled with effects of suggestion—may be why the drug experience could be reported as "replacing" narcotics in dying cancer patients.) Dehabituation (ie, a response to the familiar as if it were novel) was noted in early studies of the drug in cats.[34-36]

The overvaluation of "nowness" is not unrelated to the fickle pursuit of the novel apparent in certain youth subcultures. The ability to see old and familiar events in a new light is also a facet in the poorly understood processes related to creativity. But the impairment of goal-directed efficiency and sustained focused attention carries with it the impairment of integrative and synthetic functions. Thus the mere *mergings* of sensory objects (the synesthesias, the plastic rearrangements or the clear focusing upon fine details or usually disregarded perceptual elements) or the elisions of thoughts and concepts hardly are the same as an organized building and arrangement in which "boundaries" and distinctions are essential. Sharpened or "heightened" perception and consciousness is not equivalent to adaptive perception, nor is abnormal brilliance necessarily to be equated with beauty. Indeed, the primitivization of perception seen in man [37] and animal [38] suggests vividness more than powerful discrimination of the complex. Creativity requires some facility not only for seeing but for implementing new meanings; but, as we shall stress, it is the need for synthesis—not the ability to synthesize with due account for real limits—which tends to be reinforced in the drug state.

## "Cultogenic" Effects of LSD

An important feature of the state is an enhanced dependence upon the environment for structure and support as well as enhanced vulnerability to the—now novel—surrounding milieu. With the loss of boundaries, persons or a group are used for such elemental functions as control—for helping one to know what is inside and what is outside, for comfort and for binding and balancing the fragmenting world.

With the fusion of self and surroundings, some of the strain caused by the *exertion* of personal strivings and their conflict with what is projected as harsh authority, can (for the moment) be transcended or dissolved. At the same time there is a leaning on others for structure and control. Hence, when the drugs are taken in a group setting, the breach with reality can—and must—be filled by the directive mystique and support of the group. This is, in part, why I have termed these drugs "cultogenic."

Many successful self-help groups are peer groups or form around a common flaw. If they are uncritical of weakness, less masking of inadequacy can ensue. With such arrangements, the distance between authority and the miscreant is diminished and so, too, is the inner tension. The cost is a surrender of a certain order of autonomy to the group, a certain passivity, and dependence upon the concrete presence of a group to share the burdens of initiative. The surrender of a conflictful autonomy (reflecting a prior instability, isolation, or diffusion) may be preferable to the compensatory delusional autonomy seen in proselytizers who aggressively threaten the establishment with love and drugs. Of course, a compulsive tendency to externalize the conflict with authority can be reinforced by peer-grouping. Nor are all the tribal affiliations we call groups endowed with the competence to guide; many are loose alliances based on the denied mutual despair of their members.

## Object Relations and Values

Actual persons in the environment have positive or negative value in terms of quite elemental functions, eg, as threats or as anchors in maintaining a primary self-control (quite as in the so-called psychotic transference) and intensities of affect can mercurially escalate and diminish in the absence of normal boundaries. Persons are self-centeredly seen and used—either to be clung to, or to be contemplated in terms of what essentially is a self-centered sensory, aesthetic, or ideologic frame of reference; they may become vivid objects of highly personal transferences. At best there may be a narcissistic shifting of one's relationship to others and to one's own ambitions which, as Kohut has noted,[39] can lead to outcomes which are socially valued—wisdom, humor, perspective. But such internal syntheses never guarantee socially pleasant behavior, and pathological outcomes are also probable.

### Model Psychosis in the Drug Experience

The elements of a model psychosis are present. This does not mean identity; rather it is an approach to certain processes which are variably present in both the drug state and psychoses. The conditions for either state have similarities and obvious differences (just as do dreams and psychosis).[40]

In the first hour after LSD most people refer their altered perceptions and relationships to the body and its parts; this period of changed bodily sensations and perceptions could be called hypochondriacal (with all this connotes as a prodromic symptom) or simply altered body image, depending on the context. The point is that there is a uniform change in the experience of the relationship of the body, the self, and their normal environmental coordinates.

The basis for hallucinations can be analyzed.[41] For example, what is impinging on an ongoing perception is a vivid memory of what has *just* been perceived; these coexisting images can compete for attention and thus give rise to illusions. (In our laboratories we have observed monkeys under LSD who may respond to serial stimuli as they had been trained to respond to overlapping stimuli.) This is marked usually two to three hours following 200$\mu$g or less of the drug and following the period of altered perceptions referred to the body and its boundaries. With the increasing loss of distance, such illusions can be imaginatively or regressively elaborated into hallucinations. Similarly, memories can emerge as clear images competing for the status of current reality. This failure to suppress the prior perception or memory or thought is reminiscent of what Bleuler called "double registration" in schizophrenia or what, in Rorschach parlance, is called contamination. Similarly the failure of identities and categories to be maintained underlies most of the descriptions of paralogic in schizophrenia.

The capacity selectively and relevantly to direct one's focus is impaired; allocation of the source of a feeling, a sound, a sight, or a thought becomes difficult since the distinction of inside and outside tends to diminish. Accordingly there are frequent mislocations or misconceptions—projections—of motives and sensations. This tendency is reinforced when one must exert energy to account for even slight changes in the environment; slight details not only capture attention but also can gain the patina of portentousness and are linked to the ever present threats of dissolution. The eventual outcome of this hypervigilance, inefficient scanning,[42,43] and mislocation is called paranoid behavior.

There is also a remarkably heightened sensitivity to gestures, inflections, and nonverbal sensory-motor cues which normally are in the background; however, the ability accurately to judge these cues and appropriately lodge them in context—just as in schizophrenic sensitivity—is easily impaired. The altered relationship of figure and ground also means that metacommunications fail; the context no longer predicts the relationship of parts to the whole.

Similarly the component affects can be enhanced under the drug state but are difficult to focus upon. Thus several contrary feelings coexist; or they fluctuate (just as sensations do); this is reminiscent of ambivalence. Subjects later refer to the total state as a pleasant-unpleasant experience. Those seeking mystical experience speak of heaven and hell. Euphoria mixed with tension may be seen.

Laughing or crying or both in the first three hours are common. With care, one observes that—following the initial perceptual changes referred to the body—there is a primary need for elemental tension-discharge—a welling up which requires laughing or crying for relief. Subjects *have* to laugh or cry and they *then* seem to find the appropriate setting to rationalize this.

However these experiences may be represented and symbolized, they are evolved from a groundwork entailing a coexistence, heightening, and fragmenting of component urges and feelings. Thus, changes in ego organization and capacity seem to occur first: this is usually manifest in the perception of bodily changes. A tension or need for discharge then becomes apparent; perception of affective changes and changes in the self and relationships with objects in the milieu supervene and dominate the experience. These changes in the first three or four hours underlie the varied experiences of "insight." Expectations and preconscious fantasies certainly stamp the content and even influence the capacity to exert control during the drug state, but with the loss of structure a "program" of vulnerabilities and needs seems to be "released" [44] or compelled by the drug.

The enhanced value and intense attention placed on the self, the narcissism, ego splits and regression; the loss of boundaries; the "double registrations"; the ambivalence; the heightened tension; the diminished control and problems of focus[45]; the unstable (or inappropriate) affect; all can represent the primary symptoms of a psychosis. Given this state of affairs one can see a variety of "psychotomimetic" or "psychedelic" phenomena elaborated and expressed—all of which require such basic shifts in ego organization. Whether or not the "observing ego" keeps touch with reality may be crucial to outcome, but is irrelevant to the classification of a psychotomimetic state. Catatonic schizophrenics often maintain a silent observing ego monitoring reality during their psychosis.[46]

The appearance of peak experiences (or acute psychedelic experiences) in clinical psychosis has long been documented[47]; early phases of acute psychoses often cannot be differentiated from accounts of drug experience.[16] In the hours following the acute flux, as adaptations to the first phase begin, we can note the subject's attempts to structure while still impaired by the drug. Where energy for scanning and testing the reality of unwanted input is required, delusional simplifications, ideas of reference or passionate beliefs occur and provide an economical explanatory anchorage.

We have with these drugs at least a tool with which to study the genesis and sequence of a number of familiar phenomena in psychiatry. Whether it can lead us to a better sorting and description of the varied elements which are present in the range of clinical disorders is yet unanswered; for example it is obvious that differences in outcome of LSD states depend upon specific prior strengths as well as varying circumstances. It is also obvious that a time-bound state such as a drug state cannot demonstrate symptomatic phenomena which develop over time and are embedded in confusing life circumstances.[48] Indeed, the role of these factors in symptomatology could be more readily distinguished by appropriate comparative study of clinical and drug-induced alterations of consciousness. Comparative studies of drug-induced states could also be useful in determining factors and sequences related to outcomes of such a multipotential and fluid state. Finally, it bears upon our thinking about any psychosis to recognize that—whatever the role of motivation—primary or secondary shifts in such elemental ego functions as attention and discrimination—the adaptive control of sensory input and perception[42,43]—can underlie a range of "psychotic" symptoms.

### Adaptations During the Drug State

Some persons endure all this without evident harm. The spectator ego can simply be interested in the reversal of figure and ground, the visual tricks, or—with higher doses—the spectator is entranced or totally absorbed. But with increasing dosage the experiencing ego can be overwhelmed. At any level, defensiveness can appear; the spectator shuts his eyes and a blind struggle for control may dominate. Basic attitudinal shifts, redirection of attention, projection denial, displacement, affective explosions, panic, confusion, withdrawal, or magical and delusional syntheses may be seen as persons attempt to cope. Rarely there is an acute loss of judgment or impulsive and primitive thinking manifest in attempts to fly or defy gravity which results in a concrete and fatal confrontation with the real world. One protection is *not* to fight the experiences during the drug state. An upsurge of the traditional defensive operations requires extra vigilance and may lead to temporary panic even in relatively stable people.

It is striking that when self-examination or confrontation with personal problems is the motive for illicit drug-taking, effects are not infrequently bad. Both licit and illicit drug users note that unstable surroundings or confused motives lead to "bad trips." When problems are aptly externalized or shared there is less panic and subsequent upset. Those who are unable to tolerate the flux by shifting attention from it or enduring it (or "guiding" it by delusional, mystical, or aesthetic revisions) may retreat into catatonic-like postures. Thus a certain yielding and surrender of ambition and personal autonomy helps some individuals to have a good experience; but this requires if not group support, a certain personal strength, or at least a facility. *It also requires stable groups.*

Those who are encouraged or equipped to *not* attend to the fragmented disparate elements, let them flow into the sway of a mystique, steered by latent guiding interests or memories. Thus all that occurs is given a tone—or a very diffuse direction. With higher dosages and the increasing loss of detailed focusing, the importance of guiding "sets" (music, mystique, affective expectation such as the doctine of boundless love) is enhanced. Indeed, under LSD it is the positive or negative attitudes and postures toward the ego's varied experiences which are most vulnerable to suggestion. The "maps"—the formulas and specific ideologies supplied by guides—are actively sought because of the vulnerability of the ego and the *relative* loss of synthetic and higher cognitive functions (such as goal directedness). Accordingly panic states may be "guided" by redirection of attitudes, or attention and by provision of structure.

### Summary of the Drug State

Thus we may say that in the presence of a heightened sense of awareness, there is a diminished role of the array of functions related to cognitive control and discrimination of complexities. The ego may be said to be less autonomous—less reliable—in the deployment of focused and sustained attention. It is vulnerable to being guided by a widened and more variable range of both internal and external factors. In order to anchor the drug-induced period of flux, direction of attention and basic orienting attitudes can be supplied either by the now impaired ego (with its defenses and prior expectations) or by the setting. Such expectations may be explicit and implicit, conscious *and* unconscious; accordingly, prediction and control over outcome especially in self-experimentation are inherently unreliable. Similarly, the utility, fittedness, and reliability of the setting will, in fact, vary widely.

The extent to which the experience of a specific "trip" is related to outcome requires finer study. So, too, does the fact that one good trip does not predict a second. Accurate studies in this area are important to our understanding of outcome. Nevertheless, the primary changes described are the background state from which a number of divergent outcomes and adaptations ensue—adaptations *both* during and after the drug experience. No doubt the rearrangements of reality which occur during this state produce a memorable experience, but one is reminded of Sidney Cohen's remark that most people get what they "deserve"[49] or what they are equipped at the time to experience as modified by set, equipment, and setting.

### Restoration of Constancies After the Drug

Two realities have been exposed in startling contrast—private and public reality, both of which are a part of experienced reality. Anyone who has experienced this intense episode must come to deal with it; some judgment about the significance and utility of these realms of the mind must be made. Our dreams are an episode in a sequence of states which we usually can somehow integrate into the normal fabric of living; similarly something must now be done to represent and cope with the total drug experience—nightmare, illusion, or ecstasy.

Some borrow stability from ready-made explanations or isolate the experience. Still others will decide that the experience of cosmic comprehension is equivalent to self-mastery. Still others, lacking any other means of mastery, will be compelled repeatedly and unexpectedly, to confront what was experienced. We see this in students who come in for help weeks after a trip—experiencing anxieties or brief unwanted trips in the absence of drug.[50]

The breakdown of those constancies and habits which normally smooth over the disparate details of our perceptions and actions can persist in frightful but also benign ways. One scientist experienced his peripheral vision to be enhanced during the drug state; it is not uncommon that there is an equivalence of value for what is at the periphery and what is normally perceived at the center of the visual field. He commuted daily, reading during the trip. For months after the drug, he was bothered by the telephone poles which flashed by his train window. He could no longer suppress what normally is background rather than compelling figure. Similarly, the unconscious "background" to thoughts, gestures, and feelings can emerge.

There are numerous anticipatory sets or constancies which operate to keep the body oriented in space and ready to meet the environment as we expect to experience it; the mind provides constancy wherever the sense organs deal with variability. We anticipate or correct for the images on our retina to keep the world stable and ordered; the hand stretched 8 inches before one, may appear small, though on the retina or camera it is large. Coming off a boat one may still waddle, maladaptively anticipating the roll of the ship. Such habits or sets can smooth out our perceptions and actions; but they can persist when they are not useful and lead to inappropriate and confused responses. LSD appears to affect these stabilizing perceptual anticipations. It rearranges and unbalances our ideas of order, whether the self and its defenses or perceptions are a referent.

### The Need for Synthesis and Outcome

The intensity of the drug experience manifest in the change of constancies can lead to a number of repetitive behaviors. The search for synthesis may take the form of attempts to reexperience the intensity of elements within the drug experience in order to master it, just as with the traumatic neurosis with its breaching of the "stimulus barrier." It is an old theme in psychopathology that in a state of altered consciousness in which control over awareness is diminished, there is no way to bind the intensities experienced and symptoms may ensue. Breuer (and more reluctantly, Freud) referred to this as the hypnoid state; explanations of the consequences of early pregenital experience to repetitive neurotic symptoms in later development have been placed in this context.[51]

While "bad trips" occurring without the drug may be explained in the model of the traumatic neurosis or hypnoid state, it is astonishing to see an entire sequence of heightened sensations as well as altered perceptions occurring with apparent suddenness weeks after the drug. This obviously evokes comparison with psychomotor epilepsy; but this connotation is as yet without foundation in facts. The psychodynamics preceding these lapses from reality also require close scrutiny; yet these reports appear to present us with evidence that the "barrier" against dereistic thinking and altered states (or the "switch" permitting a shift of mental states) is a factor which in itself merits intensive investigation. There are schizophrenic patients who appear eventually to have learned or discovered that there was some control which they could exert against "slipping" into such states. Whatever the explanation for either the loss or the mastery of such controls may be, it is evident that the experience of the LSD state with its intense clarity in the presence of diminished control can have a range of consequences which cannot always be anticipated simply by monitoring the apparent intensity of the ongoing drug state.

Repetitive symptoms—such as acting out—may occur. In part, these may be viewed as unsuccessful attempts to restore or find constancies and boundaries. Such behavior, which invites control and guidance, frequently appears as a provocative accusation against authority and—by provocation—preserves a tie with it. Others aggressively and endlessly talk about their experiences as if they were trying to put them together.

For some, reflection about the sharp contrast of drugged and real life may evoke mild or severe rumination and depression—related to an urge to recapture the lost illusionary and brilliant drug world. The extent to which primitive and regressive fusion fantasies will dominate these reactions varies. Conflict and confusion about "what *is* reality" or the experience of normally repressed thoughts and urges by the unprepared ego can lead to mild or severe symptomatic states, perplexity, and disorganization.

In any event, variably determined needs or capacities to cope with the split or breach of normal experience can be expected. This may be a simple "sealing over," or even an enlightened and useful thought formation we call insight. Some react with a denial of inadequacy and anxiety about loss of control; borrowing the enhanced omnipotence of the drug state, they show a delusional autonomy. This may lead to various outcomes: that of the benevolent and foolish prophet, or the defensive, alienated therapist, angry at those who prevent his curing the rest of the world. Any threat to the values of the illusory experience of union and omnipotence—such as undrugged reality—could evoke defensive denial and strident proselytizing.

It is interesting that classifications of pathological outcomes of conversion [52] (including irresponsibility and omniscience) startlingly resemble patterns we see with LSD. Indeed, we must seriously wonder why those who find salvation are so implacably generous and so ready to advertise! Implied are unsolved problems with authority figures. Salvation often involves renunciation of previous ties; those who are saved must repetitively convince others in order to diminish their own doubt, isolation, and guilt. At best, they may do this not only to share but in order to reachieve union with those from whom they have been separated by their unique vision and experience, and to synthesize these breaches with important others.

### The Role of Groups in Outcome

Some kind of continuity with the gap in reality is sought. The bridge may be a book as it was with Huxley, a silent synthesis, or change of values and tastes, or the understanding of a group or person. In the Native American Church, the Indian utilizes religious explanation and adherence, specific ceremonies, and the group with its ideology to integrate the experience which serves a purpose in the total fabric of his life.[2]

There are mixed consequences with the reliance on groups. In some chronic users one sees a bland impulsiveness—an indifference to the habitual and customary which may border on a supercilious posture of superiority. The elect of many cults either *assume* this attitude or the outsider *feels* this to be the attitude of those who know something he does not. This benign or irritating posture has also been remarked upon in the American Indian peyote users who are often a subculture not infrequently at odds with established groups. Nevertheless, the observed reliance of drug users on cults can permit at least a measure of authentic self-involvement at a level which is realistically available to the persons involved. Where these "cults" are but loosely juxtaposed cliques connected by common rationalizations, there is still some comfort and protection from a ruminative self-concern which is enhanced by isolation.

Mystical or religious representations also are remarkably apt for synthesizing the experience. Religion can relate man to his limits while taking account of his boundlessness which occurs in all aspects of this realm of the mind. It may be that religious symbolism aptly represents the transformations characteristic of this latent part of the mind. Against fragmentation and directionlessness, something coherent lends continuity to experience. Against dread, transcendent love can prevail; loving like redness can apparently be enhanced and is remembered. The "lovingness" and "strongness" of a parent can be parted from the particular persons and transcendentally represented in various forms of power ascribed to deities.

There are, then, a number of features of this multipotential state related to its intensity, its novelty, its boundlessness which account for some of the expectable occurrences within it and some of the expectable—and observed—dangers and variable outcomes.

## LSD in Psychiatry

There are a number of psychotherapists who have attempted to use the loosening of associations *and* the intense experiencing produced by the drug in order to influence behavior change in individual as well as group therapy (and the drug obviously is useful for the study of group processes).[53,54] There are a few ongoing controlled projects and a long history of experience with the use[3,55]—and abuse[56]—of LSD in therapy. In the late 1950's some physicians thought they had discovered a new reality of the mind and were not only struck by the drug-induced phenomena, but apparently addled by them. Perhaps they were simply jealous of the subject when they insisted upon taking the drug concurrently with him.

Today, two major serious modes of treatment prevail. That employed by many European workers (called "psycholytic" by Leuner[44]) represents a method by which certain defenses are breached. With a strong drug-enhanced tie to the therapist, feelings, memories, and transferences are allowed to emerge vividly and unforgettably before the eye of the consciousness and their strength discharged. The events are later worked over with care. Dosages are regulated in part by the capacity of the patient to steer a course between being utterly lost or overly constrained by habitual defenses. A kind of active participation in the presence of a general loosening is sought. As issues in therapy arise, clusters of intense affects directed towards early experiences and objects are encouraged; thus, fantasies involving rebirth, early transference strivings, and trauma can emerge with sensory intensity. The therapist lends support and later interprets.

Certainly, people are initially less guarded under the drug and can experience a range of "insights" they might normally disown. Yet they also can react quite defensively under the drug when what is seen is, for personal reasons, overly traumatic. To an extent they can ward off self-recognitions with affective outbursts and they can clearly distort them by basic attitudinal shifts, displacements, redirection of attention and projections, denial, confusion, withdrawal, or magical and delusional "syntheses."

For quite vivid self-encounters there is usually no postdrug amnesia. The integration which follows is a collaborative venture requiring the active participation and the output of the patient. During treatments, a sequence of defensive memories, transferences, and distortions commonly arises and requires further drug sessions and work. Illicit drug users also encounter "hang-ups" but have little guidance to work them through sequentially. The therapists find this absorbing and exhausting; they generally work with inpatients and severely ill or characterologically impaired patients.

In the so-called psychedelic therapies as they are now being tested, there is an awareness of an immense amount of preparation, of salesmanship with an evangelical tone in which the patient is confronted with hope and positive displays of it before he has his one great experience with a very high dose of drug. The drug experience is structured by music and by confident good feelings. With the support of the enthusiastic therapist, the patient is encouraged to see his life in a new light, to think of his future accordingly. There now tends to be a rather long period of follow-up and support before the patient is discharged. An earlier mode of intervention attempted to avoid the tangled problems of relationship between therapist and patient[10] with but a single high-dose drug session as the chief therapeutic contact; the current approach is more explicitly ritualized (in the model of nativistic movements); the person and attitude of therapist tends not to be analyzed but incorporated. It is speculated that the egocentric problems of the alcoholic may be specifically tailored for this "ego-dissolving, ego-building" technique. Other approaches, eg, employing hypnosis,[57] lie somewhere between these two. It is interesting that peyote cultures also report cures of alcoholics but the effects may not persist without sustained group support and leadership.[2] The effectiveness and selectivity of current therapies is far from settled and research is still ongoing.[3] Obviously careful follow-up is essential since the immediate glow which occurs with drug-induced personality changes in such contexts can be deceptive. The fact that under LSD the therapist can often readily suggest positive or negative attitudes toward life experiences and promote a state in which struggle *may* be diminished should arouse our fundamental curiosity not only about LSD therapy and its effectiveness, but about the mechanisms, utility, resistances, and pitfalls in behavior change achieved through persuasion.[58,59]

## The Scope and Dangers of Illicit Use

We should recall that the increasing problem of drug abuse in most countries is alcohol, followed by the barbiturates, amphetamines, opiates, and mild tranquilizers. In this context the consequences to national health of hallucinogens are not as yet truly startling—either in terms of the utility of LSD or its harm. In the long run, debates about whether or not to use LSD are hardly as socially consequential as the use of "the Pill." The agent most frequently used by youth for illicit purposes and with lethal effect is the automobile; and the most faithful monitor of the scope of such social problems is the prevailing high insurance rates for young men. The actuarial superego of our society has not yet instituted insurance rate changes for medical, psychiatric, or mortician's coverage in response to these chemicals. This is an interesting generation but they have not as yet gone completely to pot!

Not all users are youth nor are all youthful users initially unconventional and unproductive. A few current illicit self-help groups reportedly employ the drug and religion to achieve a conventional outcome; eg, a group of exconvicts and a group of homosexuals. Several religious and lay groups have set up agencies to be phoned when panics are encountered. We seem to be living in an era when many practices (half-way houses, group therapies, cathartic therapy, confrontation therapy) built into the fabric of psychiatric work are imitated by ever proliferating self-help groups which frequently tap our society's long tradition of distrust of medical science. Unfortunately, nonscientific searches for cures are too easily dismissed as fanaticism, eccentricity, or ignorant superstition. Yet these social responses in part reflect upon the ability of the health professions to deliver relevant services, to treat irrational anxieties, or to be competently aware of and responsive to the issues and consequences of different patterns of drug abuse.

Reliable estimates of the incidence of psychedelic drug "use" (however defined) are always vulnerable to criticism. They range from 1% to 15% on certain campuses. Figures higher than 5% probably do not distinguish single trials from habitual use nor LSD from other drugs of abuse; eg, proselytizers frequently tell us about the "inevitable" growing use of "marijuana *and* LSD." Only a small fraction of persons who have taken the truly potent hallucinogenic drugs could be said to constitute a reliable base for study of long-term users. Groups of persons who drift in and out of the category of users are not easy to identify and are hardly reliable reporters. The problem is that some are always first discovering the drug (available now for 20 years) and acclaiming it while the silent others are experiencing disillusion after a year or two of absorption. Still others actively seek or passively accept one or two self-experiments. We clearly require a study of the fad element in usage; cycles of interest may well be shown to follow certain press releases and to vary sharply with opportunity and the ethos of different settings—eg, hippie centers or campuses or enclaves of middle-aged imitators who mourn their lost youth. Clearly the motives for experimenting, maintaining—or self-regulating—the intake of any drug differ as do the consequences of these varied patterns of use.

Complications for research also arise from sensational publicity. The select as well as the popular press provide a structure for the curious, restless, and lost as they compete to announce or denounce drug usage. The psychedelic hucksters—for a bandwagon effect—confidently announce that growing hordes of youngsters are independently dedicated chronic users. To the mature, their message is that this is a revolution in which adults are helpless; to the young it is a subtle invitation to revolt under the sanction of inevitability. The establishment then reacts with irritation and fright. As the advertising escalates and the empirical problem indeed grows, the young and their frequently confused and permissive parents must enter the debate and assess the claims of value. Physicians hysterically crying alarm join the melee, lumping all bad reactions into one dire outcome: permanent madness. They can now also cite somatic dangers.

Reports of chromosomal changes in preparations of lymphocytes raised in tissue culture are not identical with "genetic damage" or clinical disease. Apart from unwarranted biological inferences, the reliability of such findings is not established; nor do we as yet know the relationship to dose, to common stimulants, or to drugs related by structure or behavioral effect. Similarly, a finding of LSD-induced stillbirth or stunted growth in rats is not identical to fetal anomalies or germ cell damage; effects in mice may differ; rodents may differ from man; similar reports of effects of other drugs (including reserpine) should be evaluated prior to sanctioning alarming reports about LSD. Nor does the persistence of hippocampal discharges for several weeks following LSD (in cats trained to avoid shock) indicate long-term brain changes nor brain "damage" in man; reserpine, in fact, produces more dramatic persisting effects in the hippocampus[60] and without the intervention of shock. Neither the history of folk usage of psychedelics nor the past 20 years of medical and lay use of LSD have—as yet—produced clear and reliable evidence of somatically dangerous consequences of the drug in man.

While such important research continues, caution about publicity is warranted on both scientific and humane grounds lest we further panic the susceptible. A single past indiscretion with LSD now leads to serious brooding over the shape of what the young parents fear will be a psychedelic monster. No doubt the social problems presented by LSD could easily be diminished if a clearcut somatic danger is established; we might, however, have yet to cope with this phenomenon without the aid of such facile warnings!

### Psychiatric Complications of LSD

The facts are that dangerous and tragic psychological consequences *are* now unequivocally established,[61-67] and it is just this fact which users deny (as if it were concocted to attack their autonomy and self-esteem). From our own campus experiences it appears that users who end up in hospitals with prolonged and serious psychoses are initially a quite unstable group. They are, in any event, a small group. Suicides and violence are also uncommon. More frequently one sees a transient panic occurring during the drug state from which recovery (without the administration of often complicating phenothiazine medications) occurs within 24 hours. If other than supportive and reassuring treatment is required, adequate barbiturate hypnosis or a sedative tranquilizer such as chlordiazepoxide is a simple regimen. A few visits for follow-up can be instituted when required. Others do not require hospitalization but often seek treatment because they are concerned about having taken the drug. They are upset or depressed about some of their thoughts and experiences during the drug state, or about their basic life dilemma—which in many instances is obviously serious. And a few others, as noted, may have serious "nondrug" induced panics some weeks after the drug state very much as a bad dream recurs. Occasionally a complicated history of multiple drug intake by a rootless youngster leads to a picture of toxic psychosis.

We must make a distinction between an unpleasant trip—even one which might lead to emergency room referrals—and various psychiatric complications of drug use which may or may not be contingent on a bad episode. Such unpleasant episodes have "turned off" those who try a casual experiment—a socially valuable response! When patients are brought to physicians by drugged or unstable friends, or in disorganized circumstances, physicians should be aware not only of the role of momentary panic (and the fact that any escalating panic can look like a toxic state) but of the possibility of complicated drug-taking patterns, of prior instability if not mental disorder. Similarly, we should note that classical instances of identity diffusion, of borderline phenomena and adolescent turmoil may—in contemporary life—be associated with LSD; this is hardly a basis for citing the drug as totally causal.

We now see little scare literature presenting an unevaluated snapshot of steroid psychoses, because we can now predict with more confidence what the results will be and evaluate the risk. Similarly we should—in time—become familiar with these drugs. The facts are that a fair number of people have had LSD without serious untoward effects. The majority of acute untoward reactions with LSD—while severely troublesome—are not as yet proven to be inevitably permanently crippling. The suggestibility, despair, confusion, and latent disorganization of those who unwisely take LSD is, I believe, as crucial a variable as the chemical which renders them—unexpectedly—vulnerable to more trauma than they can handle. The habitual long-term use of LSD for pleasure or escape produces the *possibility* for the impairment of good sense and maturation. In this sense, the drug can reinforce a dissociative trend, leading to acute reactions or insidious disorganization and failure successfully to integrate life crises.

## The Risk of LSD "Trips"

*Impressions* gathered from various observers indicate that the experience—though not necessarily the outcome—of approximately 10% of any batch of trips (whether or not it is an initial one) can be potentially upsetting. With skilled guides perhaps many of these potentially unpleasant experiences are warded off or redirected. With skilled therapists, 1% or less of drug experiences may be unexpectedly traumatic. Certainly under these circumstances less than 1% is traumatic in outcome. With proper immediate follow-up most of these reactions should be therapeutically resolved. This appears to have been the case even though attempts to screen subjects in order to predict reactions have not yielded clear-cut guidelines [68,69]; and it has *not* been established that the drug is necessarily traumatic when given to severely mentally ill persons with the structure and follow-up available in therapeutic settings. In all probability older subjects (past 26 years) are less likely to have prolonged reactions linked to a single bad experience.

While such impressions require research, we can be confident—from the experience at responsible research centers in the 1950's and in European clinics—that the setting and the ability to manage the experience and its aftermath are crucially important. We can also be reasonably certain that the risk differs when the drugs are taken under unsupervised circumstances; or with unwise therapists or guides; or by adolescents attempting self-analysis; or in specifically therapeutic experiences or in sensibly controlled research conditions. There is no question that good sense and trained skills can help to control bad LSD experiences and outcomes. The inescapable problem is that—excepting within narrow limits—a bad experience and an unwelcome outcome need not be associated and neither can always be predicted.

## The Drug Mystique

My current opinion is that the chief abuse of LSD is irresponsible, alluring, and provocative advertising. Havelock Ellis' enthusiastic report of the effect of mescaline,[70] while evoking alarm about possible abuse,[71] did not flower into a cult or into a topic for the bored mass media. An ideology couched in the language of drugs has been insinuated into youth culture by a band of quite articulate writers and vagrant professionals. These have replaced the old medicine show of yesteryear with an updated campus version complete with readings and tempting arguments if not pills to sell: "tune in, turn on, and dropout." A drug mystique has been welded to the underlyingly serious shifts and strains inherently experienced by the most potentially unstable group of any society—the adolescent and young adult.

We need not determine whether this is indeed a "now" generation valuing honesty, love, direct confrontation and uncomplicated action, and avoiding ideologies in favor of simple justice. These values, however germane to the LSD experience, were not born from the drugged mind. The Pied Pipers of LSD—peddling a drug which *can* enhance poor judgment—would lure youth from the acquisition of competence (or even from the serious study of man's attempts to deal with the two orders of reality in his personal development and in his religious, artistic, philosophical, and scientific endeavors).

If we make the distinction between the psychedelic mystique and issues about the utility of LSD, and if we attempt to account for the fact that the greatest abuse has been among the well-educated—or those who might be—we would in all honesty have to question the strange tolerance for these psychedelic follies in campus cultures. Forgetting both Freud and James, many of our teachers and intellectuals are either entranced or perplexed by stories of LSD-induced revelations. They appear neither to have learned from nor to teach from experience.

We seem to have forgotten that there are trained persons who in fact have more experience than the self-appointed gurus in coping with adolescent turmoil and the more serious dysfunctions. There are scholars and disciplines knowledgeable about man's attempts to understand subjective experience and its manifold aesthetic, literary, and intellectual expressions. The social psychology of groups, cults, conversion, enthusiasm, and utopias is hardly a new discipline. None of this seems to have crucially permeated our campus cultures in terms of new curricula or opportunities for both confrontation and reflection. In brief, much of this advertising may "take" because in exploring new frontiers we have lost confidence in our traditions and seem to have avoided dealing both with the rationalizations and the honest probings of the drug cultists and other youth on campus. In any event it is clear that "education" of the drug-prone young will require more than a troop of physicians. Some sophistication about the vicissitudes of man's gullibility might render our institutions less vulnerable to sophistry.

The psychedelic apologists insist they have the civil right to take any agent which does not harm others. It is, of course, hardly a private matter (and it is a civil matter) when irresponsible proselytizing—born from the spirit of oedipal revenge—leads to a number of drug-related cases in children and young adults requiring psychiatric care for either brief or long periods of time. It is often forgotten that the real momentum for such claims arose when a few psychologists who peddled the drug resented the notion that medical or even nurses training were required for the responsible administration of potentially toxic agents. The problem, of course, is that the psychedelic gurus—while promoting frenetic advertisements for themselves—are not in a position to manage the consequences of their ideological schemes. When they do admit the drug might be dangerous, they do so by insisting that only the very courageous should take the drug! The rationalizations which prevail among those who experiment with LSD are often borrowed from these various preachings.

### Motives for Use

The motives for LSD use are varied. Sociologists refer to problems of commitment and alienation and at least add thereby to the younger generation's verbal mythology. We might remember that wild analysis and "psyching"—probing into one another's supposedly unconscious motives—characterized youth of previous generations, as did self-experiments with hypnosis even in the 19th century. Curiosity about the mind, about what *can* be experienced, about who one is and is to be can be expected. All the crises of adolescence[72]—the fluidity, shift of primal objects, narcissism, somatic changes, inexperience, and identity issues—play into the drug-taking culture.

Of the college users I have studied, a "need to feel"—to gain access to themselves and others—a pervasive sense of being constricted seem characteristic. In a recent report of a group in which Rorschach and other studies were available, this *theme* dominated even though outcomes sharply differed: these ranged from psychosis, to instability, to a reaction of bemused enlightenment.[73] One wonders whether the consequences of a "boundaryless" or destructively permissive upbringing leads to a lack of distinctions, a deficient recognition of self-experience especially when drugs or authoritarianism (masked as rebellion) are common ways to achieve feeling and a sense of distinctiveness.

Some college students clearly tried the drug as part of clique activity; taking the drug puts the student one-up—he has "been there." This is a challenge evoking interest among friends and can provide the basis for a loose group cohesion. For this group, magical transformation of reality, omniscient union rather than painful confrontation of separateness and effort is a lure. Old limits can be dissolved and—with a single gulp—philosophical infants are transformed into sages. The frustration of years of inexperience are replaced by an intense arcane experience; it is as if the secrets of the parental bedroom are instantly transcended by the mysteries of the drug! The tables are turned as the young turn on; now it is the parents who stand by in perplexed, uncomprehending, and fascinated impotence.

Others sincerely feel they should confront an experience advertised to be so important. They can be dared by accounts of pleasant or assertedly profound experiences. They see the drug as an emotional fitness test, somewhat analogous to physical fitness. The issue for many is "control." They experiment with the right to drink and test their ability to stop. At this age they are doing the same often with cigarette smoking, studying, or with masturbation. In general, they are rehearsing their strength and autonomy at a time when their lives are largely unwritten. Many behaviours of this age constitute a probing for consequences—an impatient attempt to leap the barriers of time, to come to grips with life and seize the fruits and risks promised in the future, the threshold of which is now just barely visible. This underlies many of the grimmer statistics of the 18 to 25 age group, including accidents and suicide. One wonders if these represent the inevitable costs of learning the lesson of consequences, of limits, of mortality.

### Summary and Conclusions

With respect to the LSD experience, we know that many serious persons have reported some transient or even long-term value in it. There is some objective evidence that aesthetic appreciation can be enhanced; eg. an LSD group bought significantly more records for a period of six months.[74] If, though, we search for major productions of art, letters, music, or visionary insight few clear-cut monuments to the drug are available. Related to creativity, the effects of the drug do not seem to have compelled it. Huxley's greatest output preceded his mescaline states; he thereafter, as I read him, tended to write *about* drugs, not to create with them. If we ask whether there have been cultures which have eradicated mental disorders and disease with these drugs, or groups which have seen the dissolution of deviant behavior, we find some slight association but no clear-cut overall differences that I know of in the general titer of human misery. In fact, the extensive use of these drugs is often associated with some form of psychosocial deprivation—an equivalent form of which is marked privilege (as in Brahmins and college students). That private satisfactions might have been achieved, that groups with the presence of these plants and chemicals could have attained some spiritual equilibrium seems apparent, but whether no alternative means exist within a culture is another question. That startling examples of new learning or even conversion can occur cannot be denied; but that we can as yet control and systematically reinforce drug-induced insights is uncertain.

We must ask whether a stable person is really under sufficient control of his motives and shifting circumstances let alone the dosage to take these drugs as a civil right for whatever personal reasons he wishes.[75] If so, who has to care for the consequences of his misjudgments? How can the stability of religious custom protect drug-takers who have little authentic orientation to religion and unstable groups and barely reliable leaders upon whom to lean. If we learn from the effects of drugs on much simpler biological systems, some side effects of any chemical cannot be avoided. Few of the advocates of unsupervised use seem to appreciate how difficult it often is to assess risk and value in drug administration—even in the best practice of medicine and psychiatry.

We should not forget to assess the cost of sustained euphoria or of pleasure states. We can seriously wonder if man is built to endure more than a brief chemically induced glimpse of paradise. Many authors have stressed that we are endowed with mechanisms with which to filter input and structure and use the fluid and irrational components of behavior. Heinrich Klüver [76] concluded his systematic and pioneering series of neuropsychological studies of mescaline with speculations about the drug's differential action on those vast subcortical areas characterized by emotionality and variability and those anchoring sensory-motor systems which aid in constancy. The question is perhaps not so much "expanding" the mind—it is expanded enough—but to see if there are drugs (or developmental experiences) which can enhance a better and more creative coordination among these so-called regions.

Thus etched upon the variabilities of culture and personality are drugs with a certain skew toward that mystical realm of the mind which knows both psychosis and religion, both heightened and useful self-insight and impaired and distorted judgment about both the drugged and everyday world. Perhaps similarities and differences of these various chemicals and their effects could—if analyzed[23]—reveal means for finer control of these experiences —at least in terms of their intensities. The possibility or impossibility of such manipulations are questions of basic importance to our notions of how neurobehavioral mechanisms are intrinsically related and the extent and means by which they can selectively be dissociated and controlled.[17,77,78]

In general, then, it seems that we have been more awed than aided by our experience with these drugs. They still remain agents which reveal but do not chart the mental regions; to do that we must employ our mental faculties available in the undrugged state. Accordingly we should do better than simply be amazed, repeating thereby the ontogeny of past encounters with mind revealing drugs. With these drugs we could learn to analyze how behavior is organized, disrupted, and influenced and see what nature can teach us about the ways in which the chemical organization of the brain is related to the dimensions of experiencing and behaving which comprise—to use an archaic term—the study of the mind.

This is an expanded version of a lecture given at the Michael Reese Hospital and Medical Center, June 6, 1967. It is a revision of a paper, "Perspectives on the Use and Abuse of Psychedelic Drugs," published in *Ethnopharmacologic Search for Psychoactive Drugs,* D. H. Efron (editor-in-chief), US Department of Health, Education, and Welfare, Public Health Service Publication No. 1645, 1967, with the permission of the editors. Sections on the Definition of a "Psychedelic" Dimension, Model Psychosis, and the Scope of Contemporary Problems have been extensively revised and that on Inherent Problems in Ethnopsychopharmacology and the Use and Abuse of Conversion omitted. Work with the drug in man and animal over the past ten years has been supported by Public Health Service grants MH-03363, 13186, and Career Investigator Awards M-1204 and K3-18566.

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# Patterns of Response to Self Administration of LSD

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Authors of magazine articles and popular books about LSD have, until very recently, heralded primarily its beneficial effects. They have stressed its capacity to "expand the consciousness" and to open the way to greater self understanding, increased artistic powers, and in general to a richer, fuller life! (1). This popularization of the drug has resulted in widespread, indiscriminate self-administration of illegally obtained compounds reputed to be LSD. The increasing popularity of the drug and the avidity with which it is now used would appear to be a testimonial to the hopes and expections of the takers.

This situation is reminiscent in some ways of what happened to Alice in Wonderland (2):

> By this time she had found her way into a tidy little room with a table in the window, and on it (as she had hoped) a fan and two or three pairs of tiny white kid gloves, and was just going to leave the room, when her eye fell upon a little bottle that stood near the looking-glass. There was no label this time with the words "DRINK ME," but nevertheless she uncorked it and put it to her lips. "I know something interesting is sure to happen," she said to herself, "whenever I eat or drink anything: so I'll just see what this bottle does. I do hope it'll make me grow large again, for really I'm quite tired of being such a tiny little thing!"

Such curiosity sometimes has unfortunate results. In experimental work with LSD there has usually been careful screening of subjects to exclude those with unstable or psychotic personalities. In addition, the conditions of an experiment minimize the likelihood of bad reactions, such as panic or more prolonged complications. There has been careful supervision of the experimental subjects and prompt psychiatric intervention when indicated. Despite this, there are a number of reports in the literature of brief or more prolonged adverse reactions occurring as a result of an LSD experience during the course of an experiment. The incidence of these appears to be quite low; certainly considerably less than 1 percent (3).

Less is known, however, of the incidence of adverse reactions in settings where there is no screening or supervision. The only two incidence figures are those provided by Blum (4) and by Fink (5). Blum's data suggests a minimal hospitalized psychosis rate of 2 percent and indicates that the overall psychosis rate may be as high as 3.3 percent. These figures are based on a population of 300 who received LSD under institutional auspices. Two of these were LSD institutions per se. Fink, in a recently published study, reports that 2 percent of psychotics who are given LSD have prolonged adverse reactions. He feels these are separate from the ongoing psychotic process. They were related very specifically to the ingestion of LSD and showed characteristic clinical findings, different from the classical symptomatology of schizophrenia. After an initial period of confusion, they showed an exaggerated emotional and affective lability.

During the past two years, there have been an estimated 200 admissions to the Bellevue Psychiatric Hospital directly resulting from ingestion of LSD. This number does not include those who give a history of having taken LSD but who are admitted for other reasons. We would estimate, based upon a recent survey, that 5 percent of the Bellevue Psychiatric Hospital admissions have had at least one experience with LSD. Our data suggests that this is almost unheard of in the general hospital population. Of the psychiatric patients who have used LSD, 15 to 20 percent were admitted as a direct result of the LSD experience. Thus the incidence of LSD use as a cause for admission is a little less than 1 percent.

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Of this large group of admissions, we have most carefully studied three samples of LSD users. These were the first 12 patients admitted to the hospital early in 1965 (6), the first 22 successive admissions in 1966 (7), and the most recent 23 admissions. The first two samples included only patients admitted as a direct result of LSD ingestion, the last sample included all patients we were able to find in the hospital who had taken LSD. The age, sex, marital status and race of the samples are shown in Table 1. The three samples, taken at different times, are remarkably similar to each other. The median age is 22; there were almost no patients in these groups over 30. There were almost as many women as men. This sex distribution differs significantly from that reported in most other addiction problems, such as with the opiates or with alcohol. Although less than 10 percent of the LSD takers were married at the time of admission this may be primarily a function of their relative youth. In contrast to the Bellevue Psychiatric Hospital population there were almost no Negroes or Puerto Ricans in this group. In striking contrast to both the Bellevue population and the public stereotype of the drug addict, they tended to come from a middle and upper socio-economic group.

**Table 1.–VITAL STATISTICS OF LSD USERS ADMITTED TO BELLEVUE PSYCHIATRIC HOSPITAL**

| | Sample I<br>Early 1965<br>N = 12 | | Sample II<br>Early 1966<br>N = 22 | | Sample III<br>Late 1966<br>N = 23 | | Combined<br>N = 57 | |
|---|---|---|---|---|---|---|---|---|
| Age—in years | | | | | | | | |
| median | 23 | | 21 | | 22 | | 22 | |
| range | 18 - 32 | | 15 - 43 | | 16 - 33 | | 15 - 43 | |
| Sex | N | % | N | % | N | % | N | % |
| male | 7 | 58 | 11 | 50 | 14 | 61 | 32 | 56 |
| female | 5 | 42 | 11 | 50 | 9 | 39 | 25 | 44 |
| Marital Status | | | | | | | | |
| married | 1 | 8 | 2 | 9 | 2 | 9 | 5 | 9 |
| unmarried | 11 | 92 | 20 | 91 | 21 | 92 | 52 | 91 |
| Race | | | | | | | | |
| white | 12 | 100 | 21 | 96 | 20 | 88 | 53 | 93 |
| negro | 0 | 0 | 1 | 4 | 2 | 8 | 3 | 5 |
| oriental | 0 | 0 | 0 | 0 | 1 | 4 | 1 | 2 |

Table 2 presents the number of times that LSD was taken by these patients. This ranges from a single experience resulting in hospitalization to claims of several hundred experiences (coded to top level of 100) before ingestion resulted in hospitalization. Of the third sample, which includes all patients in the hospital who had taken LSD, seven took the drug only once before hospitalization.

**Table 2.–NUMBER OF TIMES LSD WAS TAKEN**

| # of LSD Experiences | Sample I<br>Early 1965<br>N = 12<br>N | %  | Sample II<br>Early 1966<br>N = 22<br>N | % | Sample III<br>Late 1966<br>N = 23<br>N | % | Combined<br>N = 57<br>N | % |
|---|---|---|---|---|---|---|---|---|
| 1 - 5 | 8 | 67 | 10 | 46 | 13 | 56 | 31 | 54 |
| 6 - 10 | 2 | 17 | 2 | 9 | 3 | 13 | 7 | 12 |
| 11 - 30 | 1 | 8 | 4 | 18 | 4 | 17 | 9 | 16 |
| 31 - 100 | 1 | 8 | 6 | 27 | 3 | 13 | 10 | 18 |

We are able to say little about the dosage of LSD taken by these patients. It was usually taken as a sugar cube impregnated with the drug. The users' estimates of the amount ingested have ranged from 100 to 5,400 micrograms. Most patients claimed to have taken 400 to 600 micrograms each time. However, without chemical identification we are unable to be sure that they have actually ingested LSD.

Almost all of the patients who had ingested LSD had previously taken marijuana. Almost all had experimented with amphetamines or another of the stimulant drugs. In addition, many had taken barbiturates and one of the opiate derivatives. They appeared to use drugs in an attempt to embrace life rather than to get away from it. Drugs gave them a sense of liberation from conventional culture and a feeling of having undergone genuine experiences.

Although LSD is publicized for its beneficial effects, a surprisingly small number of our LSD takers said they took the drug primarily for these benefits. Only two of our first 34 patients took LSD to achieve personality improvement via psychedelic experience. Fourteen sought "kicks" or "highs." The rest, although primarily interested in excitement or companionship, said they would not have minded being helped psychologically in addition to achieving an experience. Almost all of these patients had some degree of personality disorder before taking the drug.

### Syndromes

Although the patients were admitted for a variety of reasons, it is useful to distinguish three somewhat overlapping categories. We have previously described these as panic reactions, reappearance of drug symptoms without reingestion of the drug, and overt, prolonged psychosis. Cohen (8) has suggested a somewhat more complex classification, with major classifications of psychotic disorders, nonpsychotic disorders, and neurologic complications. We would, at this time, suggest a classification of acute reactions; recurrent reactions, in which there is a return of symptoms without reingestion of the drug; and prolonged reactions.

Table 3 is a compilation of the number of patients with each of these syndromes in our first two samples. There were no significant differences between the patients in each of the classifications with regard to any of the patient characteristics previously described. A number of the patients first appeared with acute reactions and later returned to the hospital because of recurrent drug symptoms without reingestion of the drug. This accounts for the number of reactions being larger than the N of the sample.

**Table 3.—NUMBER OF PATIENTS HAVING EACH TYPE OF RESPONSE**

| | Sample I Early 1965 N = 12 | Sample II Early 1966 N = 22 | Combined N = 34 | |
|---|---|---|---|---|
| Type of Reaction | | | N | % |
| Acute | 7 | 11 | 18 | 53 |
| Recurrent | 3 | 8 | 11 | 33 |
| Prolonged | 3 | 8 | 11 | 33 |

#### ACUTE REACTIONS

The acute reactions arise with ingestion and are short lived. They include psychotoxic and panic reactions. Fifty-three percent of the patients admitted as a result of LSD ingestion presented with such acute reactions.

*Psychotoxic Reactions*—This group includes those Cohen has labeled acute paranoid states as well as patients who show evidence of confusion. These are transient episodes not extending beyond the period of activity of the drug and the symptoms appear to be closely related to the direct action of the drug. For example, in response to grandiose or persecutory delusions the individual may expose himself to danger. This was seen in the case of a young man who thought he was invulnerable and walked up the center of 5th Avenue against traffic. He was brought in by the police. In other cases an individual may be unable to cope with conflictual material that may appear under the influence of LSD. A man in his mid-thirties took LSD while mourning the recent death of his wife. Under the influence of the drug he experienced unrealistic guilt about her death and the return of a series of traumatic memories from his earlier life. While under the influence of the drug, he slashed his wrists. For both these patients lack of adequate supervision during the period of drug action resulted in behavior which was dangerous to themselves or others. Those patients who show confusion at the time of admission have only an indistinct memory of their LSD experience.

*Panic Reactions*—Panic is often seen at some stage of the LSD experience. Whereas the symptoms in the psychotoxic reactions appear to be the direct effects of the drug, panic appears to be the response of the individual to the drug induced symptoms. In our patient population, panic reactions occurred both in the novice taking his first trip and in the more experienced drug user. The patients present with overwhelming anxiety, fear of going crazy, a sense of helplessness and loss of control. They are often afraid they will not return to their pre-drug state. Both the setting in which the drug was taken and the psychological state of the person at the time of ingestion were important in precipitating panic. A confused, chaotic or lonely setting, or anxiety or depression at the time of taking the drug, are more likely to result in a panic reaction. Some patients came to the hospital themselves seeking relief from their terror; others were brought by friends who felt they could not control the patient or could not prevent him from harming himself. One person cut his wrists in a suicide attempt; another jumped or fell from a window.

A subgroup within the panic reactions consists of those patients who have been given LSD without their being aware of it. Under these circumstances even those patients who have previously had LSD may experience panic. One patient expressed this as, "Now I'm experiencing this without taking the drug. I must really be going crazy." She then came to the hospital.

Recovery from these acute psychotoxic and panic states was rapid, usually within three days. In our experience a supportive environment and a sympathetic nurse are adequate for the treatment of these patients. When these are available, medication has not seemed necessary and we have hesitated to add another variable to a drug induced state about which we know so little.

### RECURRENT REACTIONS

The spontaneous return of perceptual distortions or feelings of depersonalization occurred in one-third of our patients. These were similar to those previously experienced under the influence of LSD. They occurred up to a year after the last previous use of the drug without further ingestion of it. They varied in length from a few seconds to 30 minutes, from transient "aesthetic" experiences to trancelike states occurring sufficiently often to interfere markedly with the individual's reality adaptation. Recurrence tended to appear in those individuals who had been preoccupied with the effect of LSD upon them before the experience, and who thought of it often. Although some patients enjoyed their newly found "aesthetic" appreciation, others became terrified when they became aware that the symptoms were no longer dependent on drug use or even closely related to previous ingestions. It was our impression, and that of the patients, that recurrent symptoms were correlated with periods of stress or anxiety. The frequency of their appearance appears unaffected by the administration of phenothiazine compounds.

### PROLONGED REACTIONS

One-third of our patients presented with prolonged reactions. These include chronic anxiety states and chronic psychotic states. Although sometimes descriptively identical with similar states (e.g., depression, schizophrenia) unrelated to the ingestion of LSD, these patients' symptomatology is most often colored by the LSD experience. They show a preponderance of visual phenomena, depersonalization, and body image distortions.

*Chronic Anxiety States*—These appear to be common and may be accompanied by depression, somatic symptoms, and difficulty in functioning. However, the individual remains in contact with his surroundings and reality testing is not grossly impaired. In our experience these chronic anxiety states may last many months and are relatively resistant to the phenothiazine drugs and to other medication, as well as not responding well to psychotherapy.

*Psychotic States*—Three of the patients who developed extended psychoses were not felt to have been psychotic prior to ingestion of LSD. The patients who did become psychotic had expected increased self understanding from taking LSD. They considered the recent experiences to be more vivid and of greater personal significance than anything they had previously known. Feelings of terror were rapidly replaced by ecstasy. In the isolation of the transcendental state they believed that they had achieved a resolution of their problems; they felt they had achieved a new self. As the effects of the drug wore off these patients were faced with the problem of returning to the real world and accommodating to it. Conflict arose as they found that their new understanding was not readily grasped or responded to by others. Rather than give up their new self, the psychotic patients strove to maintain their sense of uniqueness, and withdrew from the world. These reactions respond to treatment as do similar reactions unrelated to LSD ingestion.

### OTHER CHANGES

Many of our patients in each of these categories showed a general alteration of values of the sort that Cohen has included in his subgroups—"dissocial reactions" and "antisocial reactions." For example, many patients felt a lessening of ambition. This was often accompanied by the formulation that life is a game. Withdrawal from competition and social interaction followed. To some a downward movement in the social scale was justified by the insight and empathy they felt they had derived from taking LSD.

Despite their unfortunate experiences with the drug, nearly 40 percent of the patients claimed beneficial effect from their transcendental experience; however, 20 percent emphatically said they felt worse after taking LSD. We were able to find no objective evidence for such claims as "increased insight" or "greater love of fellow man." Most of the women said they felt less social constraint after taking LSD, one going so far as to change her occupation from office work to prostitution. In the literature on LSD the effects of the drug are described in great detail, and in addition, communication between users further serves to disseminate knowledge about typical reactions. It is difficult to find an uninformed user. The role of anticipation and expectation colors both the experience and its interpretation and makes it difficult to evaluate these claims.

## Comparative Survey

A recent survey of 102 randomly selected psychiatric hospital admissions and 48 randomly selected general hospital admissions may be used to compare these groups with the people who use LSD. Table 4 presents the age, sex, marital status and race of these groups as well as the combined LSD group presented earlier.

The groups differ in a number of ways. It is clear that those who use LSD are considerably younger

**Table 4.—VITAL STATISTICS OF THREE PATIENT SAMPLES**

| | General Hospital N = 48 | Psychiatric Hospital N = 102 | LSD Users N = 57 |
|---|---|---|---|
| Age—in years | | | |
| median | 44 | 33 | 22 |
| range | 16 – 60 | 16 – 80 | 15 – 43 |
| Sex | % | % | % |
| male | 73 | 55 | 56 |
| female | 27 | 45 | 44 |
| Marital Status | | | |
| single | 71 | 82 | 91 |
| married | 29 | 18 | 9 |
| Race | | | |
| white | 62 | 60 | 93 |
| negro | 33 | 37 | 5 |
| other | 4 | 3 | 2 |

than the other hospital populations studied. There is a preponderance of whites among the LSD users. Although not included in this table, it should also be noted that in marked contrast to the Bellevue population there were no LSD users who had been born in Puerto Rico. The psychiatric hospital population and the LSD users had the same percentage of men and women. In contrast to the other Bellevue Hospital samples the LSD users tended to come from middle and upper socio-economic groups. These last two are in striking contrast to the usual stereotype of the drug addict as a male from the lower socio-economic group.

Table 5 is a summary of the drug histories of these populations. The randomly selected psychiatric hospital sample has been divided into those who have and those who have not used marijuana. Analgesics and antacids are used primarily by the general hospital population. Laxatives are used less by those who take LSD. There appears to be little difference in the use of alcohol and tobacco between the various populations. There is a consistent increase in the use of stimulants, sedatives, narcotics, marijuana and the major hallucinogens, as one proceeds from the general hospital population to the psychiatric population who have not used marijuana, to those who have used marijuana; and finally to those who have taken LSD. This is most striking for the stimulants. None of the general hospital population had used them in contrast to 91 percent of those who had taken LSD. Almost one-half of the hospitalized patients who used marijuana or LSD also had used one of the opiate derivatives. The difference in marijuana use by the general hospital and psychiatric hospital populations is greater than appears in the table. Of the 10 percent of the general hospital population who used marijuana, most had used it only once or twice. Most of the 30 percent of the psychiatric hospital population who had used it had done so on many occasions.

**Table 5.—DRUG USE HISTORY**

| Drugs | General Hospital N = 48 % | Psychiatric Hospital Population | | |
|---|---|---|---|---|
| | | without marijuana N = 72 % | with marijuana N = 30 % | LSD Users N = 23 % |
| Analgesics | 73 | 64 | 53 | 43 |
| Antacids | 60 | 21 | 37 | 26 |
| Laxatives | 33 | 44 | 43 | 17 |
| Alcohol | 71 | 83 | 90 | 74 |
| Tobacco | 77 | 78 | 83 | 83 |
| Stimulants | 0 | 10 | 47 | 91 |
| Sedatives | 17 | 25 | 43 | 65 |
| Narcotics | 6 | 4 | 43 | 47 |
| Marijuana | 10 | — | 100 | 96 |
| LSD and Mescaline | 0 | 1 | 16 | 100 |

If one examines the drug histories of those who have utilized marijuana or LSD, it is different from the usual stereotype of the drug addict. The classic drug addict is reported to utilize opiates exclusively or with occasional use of barbiturates as substitutes. The hallucinogen user is the drug equivalent of polymorphous perverse. He is drawn to experiment with any drug which has major central nervous system effects.

## Conclusions

1. The patients admitted to the hospital with a history of ingestion of LSD appear to be a population significantly different from both the general hospital and psychiatric hospital population. They also differ from the classically described opiate addict or alcoholic. The composite LSD taker admitted to the hospital might be described as a 22-year-old white man or woman with one year of relatively unsuccessful college work. He is likely to have come from a lower middle class family and to have some history of rebellion against family norms. He has taken LSD for "kicks" or experience rather than for self-improvement. He will previously have experimented with marijuana, amphetamines, and perhaps a barbiturate or an opiate.
2. These patients present with one of a variety of syndromes of an acute, recurrent or chronic sort.
3. Although some of these patients claim subjective improvement as a result of their drug use, there has been no objective evidence of this change in our selected sample of patients hospitalized for ingestion of LSD.

Our continuing evaluation of the results of taking LSD substantiates our earlier impression that it is a potentially dangerous drug when self administered. Because these are clinical observations rather than well controlled experiments, we have little information about these patients' predrug state. The changes we observed may represent the natural course of an ongoing neurotic or psychotic process.

However, LSD appears to be implicated for several reasons: (a) We have reasonable evidence that they actually took the drug; (b) it seems to have played at least a precipitating role in their admission to the hospital; and (c) the drug experience appears to have colored their ongoing psychiatric difficulties. The exact nature of the relationship between the drug and the reaction remains to be explored.

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# Harmful Aspects of The LSD Experience

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Why is it that some people, sometimes after only one lysergic acid diethylamide (LSD) experience, become victims of depression, paranoia, psychosis and even suicide, whereas others, even after numerous LSD sessions, appear to suffer no ill effects but often even claim substantial benefits in personal insights, functioning and creativity? Prolonged adverse reactions to LSD usage have been reported and classified by Cohen and Ditman (4), more recently by Frosch *et al.* (8) and by Ungerleider and Fisher (13). Conversely, there has been considerable interest in the use of LSD as an adjunct to psychotherapy and as a means to further creativity (1, 2, 5, 12).[5] How can this apparent paradox be explained?

It occurred to the authors that an understanding might be found by exploring the nature of the drug experience in those people who suffered ill effects from their LSD sessions and comparing it with that of those people who claimed no harm. To this purpose, a standard card sort of 156 items descriptive of the LSD experience, a number that allows that experience to be evaluated quantitatively, was retrospectively administered to LSD users who required psychiatric care (either hospitalization or outpatient treatment) and to a number of other users of the drug who did not require treatment.

## Procedure

### Subjects and Groups

We selected subjects who had reported taking LSD one or more times and were willing to be interviewed for pertinent biographical data and then be administered the card sort, as a means of describing their drug experience(s). In all, 116 subjects participated in the study, all of whom were seen by trained interviewers who obtained the needed biographical information and administered the card sort. There were 98 men and 18 women, ranging in age from 15 to 47. Occupations varied from unskilled laborer, student, housewife, artist, to professional people. The number of times the drug was taken ranged from once to well over 100 times for an individual. The dosage reported varied from 75 to 1500 μg, but the dosage can be considered as only a poor approximation, since the drug was usually obtained from illicit sources. However, our experience with controlled dosage studies leads us to believe that these subjects ingested enough of the drug to have a "massive LSD alteration of consciousness."

Subjects were divided into the following 3 groups:

*Group I:* The largest in number, this group consisted of 52 persons, none of whom needed psychiatric care because of his LSD experience(s). This group is of considerable interest, because the great majority were functioning at the time of testing, either at jobs or as students. In addition, many reported having had several drug experiences. This group was recruited through a variety of community contacts, including students, patients, and colleagues.

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[5] Personal communication, S. Grof, 1966.

*Group II:* This group consisted of 27 subjects who applied privately or to clinics for psychiatric outpatient care, apparently as a result of their LSD experiences. Here, too, the majority were employed at the time of testing, and reported multiple drug experiences.

*Group III:* This group consisted of 37 subjects in psychiatric hospitals in the Los Angeles area, where they had been hospitalized as a result of their LSD sessions. Again, multiple LSD experiences were reported, but unlike groups I and II, many of these subjects were unemployed.

### TEST INSTRUMENTS

In the interview, biographical information regarding age, sex, education, employment, number of LSD experiences, approximate dosages, and histories of drug taking was obtained. The "DWM card sort," containing 156 items descriptive of the LSD experience, was originally designed and assessed by three investigators (Ditman, Whittlesey and Moss (5, 6)) over a period of 9 years. Originally over 300 items were compiled, which seemed to exhaust descriptions of the LSD experience. This original card sort had been administered to more than 200 subjects, who were asked to rate each of the items on a five-point scale, ranging from "very much like the experience" to "very much unlike the experience." Gradually those items which did not seem relevant or did not evoke a differential response were eliminated, and duplications were dropped. The remaining 156 items were classified into the following 12 categories: 1) strong pleasant emotions (17 items); 2) self-understanding and aesthetic appreciation (20 items); 3) mystical and paranormal sensations (14 items); 4) empathy (6 items); 5) religious feelings (7 items); 6) unusual body sensations and perceptions, not unpleasant (33 items); 7) somatic discomfort (12 items); 8) depression (7 items); 9) paranoia (6 items); 10) anxiety (19 items); 11) hallucinations (6 items); and 12) evaluation of the experience (9 items).

The DWM card sort, with its 156 items listed under 12 categories, is furnished in Appendix A.

## Results

### BIOGRAPHICAL DATA

Table 1 provides a comparison of the three groups in relation to levels of functioning, frequency of LSD usage, and drug histories. Surprisingly, frequency of LSD usage shows no significant difference among groups: 35 percent of the subjects in group I reported 25 or more sessions with LSD, as against 38 percent in group III. And the percentage of subjects who reported taking the drug only once is relatively small *in all groups*—from 25 percent in group I to 11 percent in group III.

Similarly, drug histories reveal almost parallel percentages across groups. It is pertinent, if odd, that there is a high percentage in all groups of multi-drug users: 53 percent in group I, 67 percent in group II, and 63 percent in group III. In other words, over half the people in all groups (and thus, in this population) reported casual to frequent usage of various drugs: stimulants, sedatives, tranquilizers and hallucinogens. Apparently this study sampled "the drug culture." However, it is pertinent to point out that the *only* group reporting a history of "hard narcotics" usage is the hospitalized group, with 23 percent in that category so reporting. We wonder whether the use of hard narcotics (or personality factors) contributed to their hospitalization.

**Table 1.—COMPARATIVE DATA ON GROUPS STUDIED**

| | No Treatment Group I (N = 52) | Outpatient Group II (N = 27) | Hospitalized Group III (N = 37) |
|---|---|---|---|
| Levels of functioning | | | |
| Working in jobs or as students* | 44 (88%) | 16 (62%) | 11 (39%) |
| Unemployed* | 6 (12%) | 10 (38%) | 17 (61%) |
| Unknown | 2 | 1 | 10 |
| LSD usage | | | |
| 1 session | 13 (25%) | 5 (19%) | 4 (11%) |
| 2 to 24 sessions | 18 (35%) | 16 (59%) | 19 (51%) |
| 25 or more sessions | 18 (35%) | 6 (22%) | 14 (38%) |
| Drug history | | | |
| Only LSD | 10 (20%) | 0 (0%) | 2 (5%) |
| Marijuana and LSD | 14 (27%) | 8 (33%) | 3 (9%) |
| Multi-drug use | 27 (53%) | 16 (67%) | 22 (63%) |
| Narcotics use | 0 (0%) | 0 (0%) | 8 (23%) |
| Unknown | 1 | 3 | 2 |

* The difference between group I and group III is significant beyond .001 level.

Finally, the percentages of persons functioning at work or as students decreases from 88 percent in group I to 39 percent in group III. A chi-square test shows that this is a significant difference, well beyond the .001 level of probability. Before drawing conclusions from these data, we should note that the level of functioning was assessed just prior to the interview or hospitalization and not before the LSD experience (s).

### Card Sort

For purposes of evaluating the LSD experience quantitatively, each of the 156 items of the card sort was rated on a five-point scale, with the following numerical values: 1 = very much like the experience; 2 = a little like the experience; 3 = neither like nor unlike the experience; 4 = a little unlike the experience; 5 = very much unlike the experience. Each subject scored all of the items from 1 to 5, according to his reported experience (s) with the drug. For each of the three groups of subjects, it was then possible to obtain the mean response for each item. One-way analysis of variance was used to determine the specific significant differences which occurred in the nature of the LSD experiences, as described by the three groups.

The most relevant finding in the card sort analysis is that of the 16 items significant beyond the .01 level of probability, 10 items were characterized by strongly disruptive emotions (see Table 2). And on all 10 of those items, subjects in groups II and III—all of whom required psychiatric care as a result of their LSD experience (s)—described significantly more unpleasant emotional feelings in their drug sessions than did those in group I, who required no treatment after their LSD experiences.

In all, 41 items differentiated groups significantly beyond the .05 level of confidence. Seven of these items were from the anxiety category. They are:

| | |
|---|---|
| "I felt I might become permanently insane." | ($p < .001$) |
| "I felt on the fringes of sheer horror." | ($p < .01$) |
| "I kept thinking terrible thoughts." | ($p < .01$) |
| "I became afraid I might die." | ($p < .01$) |
| "Certain things did frighten me." | ($p < .05$) |
| "I felt something dreadful was about to happen." | ($p < .05$) |
| "I was disgusted by some sexual ideas that came to mind." | ($p < .05$) |

In addition to these fears, treatment groups II and III reported far greater intensity of feelings of despair and hopelessness than did the nontreatment group I. Surely it is pertinent that of the seven items in the depression category, five items significantly discriminated these groups:

| | |
|---|---|
| "I felt like committing suicide." | ($p < .01$) |
| "I felt as if life had lost its meaning." | ($p < .05$) |
| "Everything seemed hopeless." | ($p < .05$) |
| "I had a feeling of complete despair." | ($p < .05$) |
| "I felt that life was not worth living." | ($p < .05$) |

Furthermore, three of the six paranoia category items distinguished the treatment groups from the nontreatment group; groups II and III reported all three items with greater intensity than did group I:

| | |
|---|---|
| "At times I had the sensation of someone spying into my mind." | ($p < .05$) |
| "I felt that other people were influencing my thoughts." | ($p < .05$) |
| "At times I felt as if I were being persecuted." | ($p < .05$) |

Anxiety, depression, and paranoia were also reported with far greater intensity by the treatment groups II and III than by the nontreatment group I. It might be interpreted, on the basis of these findings, that the characteristics of the harmful LSD experience include such specific concerns as imminent death, disgusting sexuality, permanent insanity, despair to the point of wishing for suicide, and persecutory paranoid ideation. These devastating emotions, experienced in a nonmedical and perhaps nonsupportive setting, might be presumed to precipitate the need for psychiatric treatment.

In contrast, these five items, which reflect a positive, beneficial experience, were reported more strongly by the nontreatment group I than by either of the other groups:

| | |
|---|---|
| "I am much more satisfied with life in general now." | ($p < .01$) |
| "I can remember very clearly everything that happened during the experience." | ($p < .01$) |
| "I have been greatly helped by the experience." | ($p < .01$) |
| "I would like to try this again." | ($p < .01$) |
| "I felt more alert and alive than I have in a long time." | ($p < .05$) |

Generally, it might be concluded that the nontreatment group experienced more beneficial, constructive sessions than did the treatment groups.

Further analysis of the individual groups reveals interesting differences between the outpatient group

Table 2.—ITEMS DIFFERENTIATING THE LSD EXPERIENCE

| Rank | Statement No. | Statement | Probability |
|---|---|---|---|
| 1 | 18 | I felt I might become permanently insane. | $< .001$ |
| 2 | 138 | There was humor and a jolly atmosphere. | $< .001$ |
| 3 | 99 | I felt like committing suicide. | $< .01$ |
| 4 | 70 | I feel as if I "missed the boat" or somehow failed to get out of the experience what was potentially there. | $< .01$ |
| 5 | 7 | I felt on the fringes of sheer horror. | $< .01$ |
| 6 | 33 | I am more satisfied with life in general now. | $< .01$ |
| 7 | 53 | I can remember very clearly everything that happened to me during the experience. | $< .01$ |
| 8 | 75 | Certain things did frighten me. | $< .01$ |
| 9 | 76 | I have been greatly helped by the experience. | $< .01$ |
| 10 | 78 | I kept thinking terrible thoughts. | $< .01$ |
| 11 | 133 | I would like to try this again. | $< .01$ |
| 12 | 47 | This was like a bad (alcohol) hangover. | $< .01$ |
| 13 | 31 | I felt something dreadful was about to happen. | $< .01$ |
| 14 | 106 | I learned what it is like to be really dead. | $< .01$ |
| 15 | 137 | Everything seemed too bright, too harsh, too loud. | $< .01$ |
| 16 | 159 | I felt closer to God. | $< .01$ |
| 17 | 109 | I felt as if life had lost its meaning. | $< .05$ |
| 18 | 141 | The experience was nothing unusual. | $< .05$ |
| 19 | 101 | I felt as if I were traveling in time. | $< .05$ |
| 20 | 124 | Everything seemed hopeless. | $< .05$ |
| 21 | 34 | One side of my body felt different from the other side. | $< .05$ |
| 22 | 88 | I was disgusted by some sexual ideas that came to mind. | $< .05$ |
| 23 | 153 | I had a feeling of complete despair. | $< .05$ |
| 24 | 36 | I saw myself as I really am, and I did not like what I saw. | $< .05$ |
| 25 | 59 | I became afraid I might die. | $< .05$ |
| 26 | 39 | At times I had the sensation of someone spying into my mind. | $< .05$ |
| 27 | 144 | Words had strange new meanings. | $< .05$ |
| 28 | 4 | I felt supremely happy. | $< .05$ |
| 29 | 86 | I felt that other people were influencing my thoughts against my will. | $< .05$ |
| 30 | 61 | I felt that life was not worth living. | $< .05$ |
| 31 | 6 | I felt more alert and alive than I have in a long time. | $< .05$ |
| 32 | 108 | I felt as I do when I need a drink (alcohol). | $< .05$ |
| 33 | 29 | At times I felt as if I were being persecuted. | $< .05$ |
| 34 | 74 | Hours went by like seconds—or one second seemed to last forever. | $< .05$ |
| 35 | 119 | Everything seemed to have a place in life, even the "good" and "bad." | $< .05$ |
| 36 | 69 | It was an experience of great beauty. | $< .05$ |
| 37 | 80 | I kept thinking of my problems. | $< .05$ |
| 38 | 44 | In the future, the appreciation of beauty will play a greater part in my life. | $< .05$ |
| 39 | 72 | I understood some things far better than before. | $< .05$ |
| 40 | 90 | I felt drowsy. | $< .05$ |
| 41 | 46 | I felt that I knew what would happen before it did—like being a jump ahead of time. | $< .05$ |

II and the hospitalized group III. The outpatient subjects showed more intense anxiety in relation to permanent insanity, terrible thoughts, and fear of death, whereas the hospitalized subjects reported greater feelings of hopelessness and paranoia (specifically, the desire to commit suicide, complete despair, and feelings of persecution). It might be construed that the outpatient group, with its stronger anxiety about permanent insanity, indicated enough contact with reality to seek help. But the hospitalized group seems to have crumbled under the impact of the drug experiences, so that its subjects could no longer defend against the powerful emotions of depression and paranoia. Actually, this vulnerability of the hospitalized subjects seems to extend all along the continuum from despair to ecstasy. For example, the hospitalized group III reported about the same degree of emotion as the nontreatment group I on these items:

| | |
|---|---|
| "There was humor and a jolly atmosphere." | ($p < .001$) |
| "I felt closer to God." | ($p < .01$) |
| "It was an experience of great beauty." | ($p < .05$) |
| "I felt supremely happy." | ($p < .05$) |

Such extremes of feeling—from euphoria to dysphoria—are typical of the unstable personality. It is conceivable that the unsupervised LSD experience could regress such personalities into acute psychotic episodes. The one item which most significantly differentiated the treatment groups from the nontreatment group is

"I felt I might become permanently insane." ($p < .001$)

Actually, this item, which heralded psychological difficulty to come, was felt more keenly by the outpatient group than by the hospitalized group. Again, this might be construed as an indication that those victims of a bad LSD experience who felt the danger of permanent insanity were still in enough contact with reality to seek therapy—whereas those who suffered depression and/or psychotic episodes as a result of their experience had lost the capacity to test the bounds of reality. Actually, it was found impossible to test these patients during the first few days of hospitalization because of their lack of contact.

Finally, these two items, significant beyond the .05 level of probability, are provocative:

"I felt as if I were traveling in time."

"I felt I knew what would happen before it did—like being a jump ahead of time."

The treatment groups experienced both of these items more profoundly than did the nontreatment group. This will be elaborated in the discussion which follows.

### Discussion

Repeatedly it has been stated that the psychiatric illnesses resulting from the "massive LSD experience" run the gamut from anxiety, panic reactions, and depression, to borderline and acute psychoses—with occasional reports of suicide as well. Our data also show that the disruptive LSD experience itself is characterized by anxiety, depression, paranoia, feelings of futility and loss of reality testing. Surely such overwhelming fears as those of death, permanent insanity and disgusting sexuality could precipitate severe and sometimes prolonged psychiatric disorders. That certain people experience such intense fears under the influence of LSD has been amply illustrated in this study. However, some salient points should be considered in this context.

First, there is considerable literature extant which describes the use of LSD as an adjunct to therapy (1, 2, 5, 9–11).[5] Repeatedly in these works are reported vivid descriptions of abreactions involving "disgusting sexuality," such as incest, sadism and homosexuality, which, when interpreted by the therapist and patient, are claimed to have considerable therapeutic value. Grof[5] even reported that some patients have suffered a psychotic breakdown under LSD, usually when they were overpowered by traumatic material brought out in therapy with which they could not cope. His procedure was to let them experience the psychosis, but then, within a day or two, to provide them with another LSD session so that they could overcome the fear and experience catharsis, after which, he claimed, the therapeutic recovery proceeded rapidly. This method of LSD therapy is more extreme than that developed by Ling and Buckman (11), who combined LSD with methylphenidate (Ritalin) and claimed to achieve abreaction and catharsis without the danger of acute anxiety attacks or psychotic episodes. It might be that other techniques can be employed in therapy, such as combining LSD with other drugs to prevent or work through anxiety, to eliminate the experiencing of deep depression, suicidal ideation and psychotic breaks.

Second, other hallucinogenic drugs, such as marijuana, its more potent counterpart, hashish, peyote (mescaline) and the mushrooms (psylocibin), have been used for centuries by primitive peoples without the disastrous effects our society has observed with LSD. It has been noticed that marijuana and hashish increase appetite and have a sedative influence, whereas LSD characteristically decreases appetite and provokes sleep disturbance. It may be that there are qualitatively different psychopharmacological effects between LSD and these other drugs. Again, it is suggested that for experimental and therapeutic purposes, it might be profitable to combine LSD with sedative or tranquilizing drugs to eliminate the majority of undesirable reactions, such as panic and depression. We do have reports of panic reactions from LSD which have been successfully terminated with antianxiety drugs without subsequent discernible untoward effects.[6]

Third, it is well known that other methods of altering consciousness have produced disruptive emotional states similar to those produced by LSD. For example, sensory deprivation and sleep deprivation have resulted in many untoward effects, including dissociation, hallucinations, and even temporary psychosis. The well known "placebo effect" can also produce untoward reactions. For example, even distilled water, when injected instead of the anticipated LSD, has been known to result in a temporary psychotic state (2).[6] And of course it has been repeatedly reported that the nonmedical use of hypnosis has resulted in regression, abreaction, dissociative states, and even acute psychosis. It may be within the bounds of probability that LSD, *alone*, is not responsible for the psychiatric disorders here reported. It seems evident that the LSD experience is influenced by the individual's personality, his set and the setting, just as are the experiences with placebos, hypnosis and sensory deprivation. Such a powerful drug as LSD, with its consciousness-changing effects, can easily be destructive to an emotionally unstable person—or even to a healthy individual—in an *unsupervised setting.*

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[6] Personal communication, K. Ditman.

LSD, in sufficient dosage, seems to have the capacity to strip the individual of his defenses, intensify his awareness and thus make him more vulnerable. This capacity seems evident in the "time-loosening" aspects of the LSD experience. Orientation in time seems characteristic of the stable individual, whereas the neurotic is disturbed by the demands of time, as in many obsessions and compulsions. Thus, "traveling in time" may be, for the emotionally unstable person, an especially stressful experience.

Further, in this study it was significant that persons functioning in jobs or as students just prior to testing were far less likely to be psychiatrically disturbed by their LSD experiences. If similar levels of functioning also existed in these persons *prior to their LSD use,* then this suggests that a person committed to a regular program of activity (other than drug taking) is somehow less likely to have a disruptive LSD experience. Thus, the question arises: is it the temporary situational state of being unemployed and unoccupied which helps trigger the bad LSD experience—*or* is it an already existing psychiatric malfunction (of which the lack of employment is merely a symptom) that renders the person more likely to have a bad LSD trip? In this regard, the role of the use of hard narcotics needs to be determined. These are areas for further study.

Still another hypothesis presents itself. Suppose the lack of regular activities in the disturbed group did not appear until *after* LSD usage (as with the "drop-outs"), then it is reasonable to assume that the LSD is part of the disruptive process, rather than a noncontributing factor. Unfortunately, for most of our sample, we do not know the actual time sequence of events.

Two findings do seem clear, however. First, in accord with previous reports, LSD in our study is likely to be disruptive for some unstable, noncommitted individuals who take the drug in a setting *without medical support and protection.* Second, there is indication from this study that the nontreatment group, many of whom describe essentially beneficial and insightful LSD experiences, supports the belief that the mind-altering properties of LSD offer potential value for research into psychotherapy and esthetic appreciation.

The latter point should not be construed as a plea for the unsupervised use of LSD! The authors deplore the messianic attitude of those LSD takers who advocate the indiscriminate (ab)use of the drug, just as much as we deplore the emotionalism and sensationalism against the drug per se, which could lead to the banishment of the drug from controlled research, despite encouraging evidence that it has value as a therapeutic adjunct and aids in the investigation of the potentials of the mind. Nor do we wish to ignore the possibilities, recently reported, that brain or chromosomal damage may result from LSD ingestion (3, 7). Certainly these reports must be intensively researched; and until they are, clinical use of LSD in human beings should be severely limited. But at this time our data on the LSD experiences of those persons who have continued to function without the need of psychiatric care suggest that the toxicity of LSD may be psychological rather than organic in origin.

## Summary

Some people have had disastrous reactions to the LSD experience, including psychotic episodes and even suicide. Others claim no bad effects, but rather benefits from their LSD usage. In an attempt to understand this anomaly, the authors studied 116 subjects from three populations: 1) those not requiring therapy after their LSD experiences, 2) those needing psychiatric outpatient care as a result of taking LSD, and 3) those hospitalized after LSD usage. All subjects were interviewed to obtain biographical data and were administered the DWM card sort (consisting of 156 items descriptive of the LSD experience), which they were required to evaluate on a five-point scale, ranging from "very much like the experience" to "very much unlike the experience." Statistical analysis revealed that the LSD sessions were far more unpleasant for those groups requiring psychiatric care than for those requiring no treatment. Specifically, the appearance of such fears as those of death, permanent insanity and disgusting sexuality and feelings of despair during the LSD experience discriminated the treatment groups from the nontreatment group well beyond the .01 level of probability. In addition, the hospitalized group experienced far more depression and paranoia than did the other groups. Interpretations of these results are offered.

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## Appendix A

1. Strong Pleasant Emotions (17 items)
    1 I could not control my laughter
    4 I felt supremely happy
    6 I felt more alert and alive than I have in a long time
    33 I am more satisfied with life in general now
    40 I had a feeling of excitement and anticipation as when something very important is about to happen
    48 I enjoyed being in this state so much that I will want it to last for days
    51 This experience was the greatest thing that ever happened to me
    52 I had wonderful sexual feelings
    83 I felt a tremendous energy
    131 I was tremendously relaxed
    138 There was humor and a jolly atmosphere
    146 I have a new capacity for love
    148 I now have more enthusiasm for things
    154 I felt in contact with unknown, wonderful forces in the universe
    155 I felt like talking it out
    157 I felt more free
    158 The whole universe was like a tremendous joke

2. Self-understanding and Esthetic Appreciation (20 items)
    12 I actually seemed to return to certain moments in childhood and experience myself there
    36 I saw myself as I really am, and I did not like what I saw
    43 It is easier now to decide what I want
    44 In the future, the appreciation of beauty will play a greater part in my life
    58 I wanted to sit and meditate
    65 I had the feeling that I have much work to do to set me straight
    68 I became more self-accepting
    69 It was an experience of great beauty
    72 I understood some things far better than before
    79 I felt more creative than usual
    85 I now have a new feeling regarding my marriage and family
    116 Things I remembered threw new light on some of my problems
    118 I felt I knew the real meaning of existence
    119 Everything seemed to have a place in life, even the "good" and "bad"
    122 I had a higher evaluation of myself
    128 I felt serene, content and knowing
    134 I was able to express how I felt without shame or care
    144 Words had strange new meanings
    145 I felt the beauty and meaning of music as never before
    150 I found I could just sit and look at something for hours

3. Mystical and Paranormal Sensations (14 items)
    23 I could make an object turn into something else just by wanting it to
    46 I felt that I knew what would happen before it did—like being a jump ahead of time
    56 The whole experience seemed to have happened before
    57 I felt as if I were several different people, only one of which was the usual "me"
    66 I felt I could communicate with others in the experience without words or gestures
    74 Hours went by like seconds—or one second seemed to last forever
    97 I felt as if I could read other people's minds
    101 I felt as if I were traveling in time
    106 I learned what it is like to be really dead
    110 I was able to influence people and objects with my thoughts
    117 I became very open to suggestion and did what I was told
    127 Past, present and future seemed to be all one
    132 I now have more belief in things like telepathy, reincarnation, spiritualism, foreseeing the future, etc., as possibilities for research
    151 I felt as if I could change past events

4. Empathy (6 items)
    24 I felt at one with those around me
    54 I felt the people here understand me
    71 I found it enjoyable when certain people were with me
    140 I am more sensitive to the feelings of others even when their feelings are not expressed
    142 The touch of someone's hand seemed important
    152 Doing something for someone else's happiness seemed easier

5. Religious Feelings (7 items)
    27 I felt a sense of wonder, joy, and peacefulness in the world
    35 I saw all the mysteries of the universe in certain objects
    50 I felt that we are all one in this universe
    64 I was on the verge of an important revelation, but not able to express it
    126 I had levels of thought I can't express in words
    159 I felt closer to God
    160 I felt as if I had been reborn

6. Unusual Body Sensations and Perceptions, Not Unpleasant (33 items)
3 My mind was flooded with thoughts
8 My hearing seemed much sharper than usual
10 The walls and floor moved and flowed
11 I felt as if I were floating in space
17 Walls or other objects seemed to be breathing
21 With my eyes closed I saw multicolored moving designs
25 Colors seemed brighter
30 Music affected my mood much more intensely than usual
32 I became another object or another person and yet remained myself
34 One side of my body felt different from the other side
53 I can remember very clearly everything that happened to me during the experience
55 I had a strange taste in my mouth
60 My thoughts kept shifting rapidly from one idea to another
67 My hands and feet felt light, or as if they were not attached to my body
73 Other peoples' faces seemed to become changing masks
92 I kept seeing things after I'd stopped looking at them
90 I felt drowsy
94 Objects seemed to glow around the edges
98 I lost interest in what I started saying so that a sentence was left unfinished
100 I was especially talkative
102 I had intense swings from "high" to "low"
103 I saw music
112 My body seemed to grow younger or older all on its own
113 I had difficulty talking
114 My sense of smell became more acute
115 I felt the need to stretch or move
123 I had "x-ray vision"
125 My body seemed to change its size all on its own
129 My "I" or "self" seemed to leave my body
139 My mind sometimes became a complete blank and my thoughts seemed to stop
143 My eyesight seemed blurred
149 I had peculiar sensations on my skin at times
196 I felt as if I had no body at all

7. Somatic Discomfort (12 items)
5 I felt unsteady and uneasy
9 I felt cold or had chills
16 I felt like I was shaking or trembling
41 My head ached
47 This was like a bad (alcohol) hangover
77 I felt hot or flushed at times
81 My stomach hurt
87 I had nausea, headache or other physical pain which dominated the experience
91 I had a craving for food
108 I felt as I do when I need a drink (alcohol)
111 My hands kept perspiring
137 Everything seemed too bright, too harsh, too loud

8. Depression (7 items)
42 I felt depressed
61 I felt that life was not worth living
89 I felt remorse over things in the past
99 I felt like committing suicide
109 It felt as if life had lost its meaning
124 Everything seemed hopeless
153 I had a feeling of complete despair

9. Paranoia (6 items)
15 People thought what I said was not important
29 At times I felt as if I were being persecuted
39 At times I had the sensation of someone spying into my mind
86 I felt that other people were influencing my thoughts against my will
104 I was worried that something within me showed what I didn't want seen
107 I resented what was being done to me

10. Anxiety (19 items)
2 I felt confused
7 I felt on the fringes of sheer horror
14 I felt anxious or tense
18 I felt I might become permanently insane
26 I felt separated from everyone and everything
28 I felt upset and distraught
31 I felt something dreadful was about to happen
37 I was easily distracted and was not able to control my thoughts
38 I felt choked or found it hard to breathe
49 I had trouble understanding what was being said
59 I became afraid I might die
75 Certain things did frighten me
78 I kept thinking terrible thoughts
80 I kept thinking of my problems
84 I tried to fight off what was happening
88 I was disgusted by some sexual ideas that came to mind
93 I couldn't keep from crying
120 My conscience bothered me
136 I felt paralyzed

11. Hallucinations (6 items)
13 I heard things that I knew were not real
19 Solid objects changed their shapes and even disappeared
62 Sounds seemed to affect what I saw
63 My own face in a mirror looked quite different; it even turned into different faces
95 I saw people or animals in motion who weren't really there
156 I saw faces or little animals coming out of the walls or other places

12. Evaluation of the Experience (9 items)
45 This experience had no therapeutic value
70 I feel as if I "missed the boat" or somehow failed to get out of the experience what was potentially there
76 I have been greatly helped by the experience
82 I now feel more ambitious
130 I felt I was not able to give myself up completely to the experience
133 I would like to try this again
135 None of these cards really can describe what I experienced
141 The experience was nothing unusual
147 There is no good reason to take such drugs

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# The "Bad Trip"—The Etiology of the Adverse LSD Reaction

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*In an attempt to identify the factors responsible for adverse reactions to LSD and to elucidate the rising incidence of hospital admissions associated with use of the drug, the authors compared 25 psychiatric inpatients hospitalized following LSD ingestion with 25 members of a group who took LSD together regularly without reported difficulty. Although some differences were found between the groups, there were no outstanding historical or current clinical features which could be used to predict an individual's response to LSD with accuracy. These findings support the hypothesis that LSD interacts with schizoid trends, unsteady reality testing, and related factors in a complex way that makes accurate prediction of response virtually impossible.*

Since approximately the fall of 1965 the incidence of adverse LSD reactions throughout the country has mushroomed. At the UCLA Neuropsychiatric Institute prior to September 1965 one problem case associated with LSD ingestion was seen approximately every two months. Beginning at that time the incidence increased gradually from five to 20 cases a month, with three to five telephone calls being received, for every person seen, from other persons in trouble from LSD who were not subsequently seen. Other hospitals throughout the country have reported a similar increase. The demographic characteristics of the first 70 such patients seen at UCLA have previously been reported (9). These patients came most often with hallucinations, followed by anxiety to the point of panic, by depression, often with suicidal thoughts or attempts, and by confusion.

The question has thus been raised why these persons should have experienced difficulty from LSD when others claim to take the drug regularly and apparently have no adverse effects. A number of pertinent additional questions are then raised. First of all, how do we know the persons who get in trouble from alleged use of LSD are really taking LSD? Since Sandoz Pharmaceuticals, the one legitimate manufacturer, discontinued production, all LSD that is available is black market, with all the impurities and dosage confusion that is attendant upon such illegal supply. Secondly, how do we know that those persons who have difficulty from LSD were not already emotionally disturbed? (In our original study 37 percent had had psychiatric care previously and 33 percent were unemployed, which were perhaps gross indices of mental illness.)

There is no applicable chemical test for LSD once it is inside the body and no pathognomonic signs or symptoms on which to make the diagnosis. Although most typically passive, the LSD user may present with almost any kind of behavior. However, beyond the history of LSD ingestion, there are no unique features although dilated pupils along with the peculiar "I feel sorry for you nonusers" smile are characteristic.

LSD users describe the perceptual changes following drug ingestion in intense and often characteristic ways. When one hears about visual and auditory "unfolding" of nature it is typical of LSD

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and other psychedelics alone. In addition, the most common side effects reported by these subjects were consistent with those described elsewhere following experimental administration of LSD (3, 4). We had several drug samples spot-checked for LSD content. Although the user always overestimated the amount of LSD in his sample, all did contain LSD (8).

The entire issue of predictability for the adverse LSD reaction is unsettled. This is particularly cogent in view of the fact that some researchers have advocated the use of LSD not only experimentally but in clinics where "creative and normal" persons could receive the drug in order to create a psychedelic experience for them. This study is a preliminary attempt to try to assess some of the factors in the etiology of the "bad trip," the adverse LSD reaction.

## Methodology

Of the previous 70 patients reported upon, 25 were hospitalized and the rest were treated as outpatients. This group of 25 inpatients, hospitalized following adverse LSD reactions, are compared in this study with 25 other frequent LSD users who reported no difficulties from the drug. This latter comparison group claimed to have ingested the drug in doses of from 250 to 1200 $\mu$g. from once to three times a week for up to 18 months. It should be emphasized that these 25 subjects were part of an existing "religious" group who took their LSD together.

We initially made contact with this group when one of their members sought us out following a lecture which two of the authors (J.T.U. and D.D.F.) were giving on the LSD situation to a community service organization in a suburb of Los Angeles. The member had initially tried to read a statement advocating unlimited use of LSD during a question and answer session following the lecture. Afterwards, he approached us and insisted that there were many persons who were taking the drug without difficulty. They had formed a group, to be referred to as the "Disciples," which consisted of 100 regulars with as many as 500 total members who met regularly and took LSD. This was before possession of LSD was made illegal in California. After we agreed to observe the group, we were "screened" by five members at the Los Angeles Airport. They were satisfied that we were not law enforcement officials and we were invited to observe some of their LSD "happenings."

Numerous subsequent visits were made to the headquarters of the "Disciples." This was located in a suburb of Los Angeles where about a dozen of the group were living in a large house on spacious grounds. They were literally tilling the soil and had decorated the house in psychedelic fashion. There were pictures of Buddha and Jesus on the walls. Every Wednesday night the group gathered to have a non-LSD religious experience consisting of prayer and meditation. The drug-taking sessions were scheduled for the weekends.

The group did not go along with the "drop out" part of the "turn on, tune in and drop out" that Dr. Timothy Leary advocates. They claimed to be working, making money, and to have rehabilitated themselves. Most of the members of the group said that they were "ex-criminals and drug addicts" who were now finding a new and useful life through LSD.

After we observed a number of their "love sessions" and all-day LSD experiences, the group agreed to psychiatric interviews, including mental status examinations and the Minnesota Multiphasic Personality Inventory (MMPI). We examined the first 25 who were available on one weekend. We then compared these data to corresponding data from the 25 hospitalized patients.

## Results

*Background.* There were no significant differences in *race, sex* or *age* between the two groups. Both groups had comparable amounts of *early parental deprivation.*[1] Both groups *resided* predominantly in the Los Angeles area.

*Marital status.* There was a highly significant difference (p less than .001) in *marital status* between the two groups. *No* inpatients were married at the time of admission to the hospital (84 percent of the inpatients had never been married) versus 60 percent married (with 19 children) in the comparison group at the time they were examined (see Table 1).

Table 1.—MARITAL STATUS

| Status | Inpatients Number | Inpatients Percent | Comparison Subjects Number | Comparison Subjects Percent |
|---|---|---|---|---|
| Single | 21 | 84 | 10 | 40 |
| Married | 0 | | 15 | 60 |
| Divorced | 2 | 8 | | |
| Other (widow) | 1 | 4 | | |
| No data | 1 | 4 | | |
| Total | 25 | 100 | 25 | 100 |

*Employment.* Only 20 percent of the inpatients were *earning a living* at the time of admission, while over 70 percent of the controls were working; this was a highly significant difference (p less than .01). The comparison subjects were mainly blue-collar workers and their jobs included those of plumber, longshoreman, gas station attendant, grocery and drug store clerk, janitor, construction worker, truck loader, tractor mechanic, aircraft plant worker, stockboy, gardener, and surfboard renter. The average length of time working was three years for this comparison group (see Table 2).

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[1] Separation from one or both parents for over six months before the age of 16 (2).

**Table 2.—OCCUPATION**

| | Inpatients | | Comparison Subjects | |
|---|---|---|---|---|
| Status | Number | Percent | Number | Percent |
| Unemployed | 13 | 52 | 5 | 20 |
| Housewives | 2 | 8 | 2 | 8 |
| Students | 5 | 20 | 0 | |
| White-collar jobs | 2 | 8 | 0 | |
| Artists | 3 | 12 | 0 | |
| Blue-collar jobs | 0 | | 18 | 72 |
| Total | 25 | 100 | 25 | 100 |

*Religion.* We could not obtain religious information for the comparison group. They had formed a new religion, and they all denied having any previous religion or that their families even had any religion. In fact they had repudiated orthodox religions totally until they "found God under LSD." Thirty-two percent of the inpatient group said they had no religion.

*Police records.* Table 3 shows the histories of criminal behaviour—64 percent of the comparison group had police histories. The major crimes that the comparison group had been involved in were forgery, stealing, carrying concealed weapons, manslaughter, grand theft auto, and aiding a fugitive. Disturbances of the peace, delinquency, minor fights, and petty thefts were classified as minor crimes. Only eight percent of the inpatient group gave histories of police records, which was a significantly smaller proportion (p less than .001).

**Table 3.—POLICE RECORD**

| | Inpatients | | Comparison Subjects | |
|---|---|---|---|---|
| Conviction For | Number | Percent | Number | Percent |
| Major crime only | | | 3 | 12 |
| Alcohol only | | | 2 | 8 |
| Drugs only | 1 | 4 | 2 | 8 |
| Minor crime only (including delinquency) | 1 | 4 | 0 | |
| Major crime plus drugs, alcohol or minor crime | | | 5 | 20 |
| Minor crime plus drugs or alcohol | | | 4 | 16 |
| None | 23 | 92 | 9 | 36 |
| Total | 25 | 100 | 25 | 100 |

*Education.* Fifty-six percent of the comparison group finished high school and an additional 16 percent had had some college education, for a total of 72 percent who were at least high school graduates. The remaining twenty-eight percent were high school dropouts. For the inpatient group 64 percent had finished high school, 32 percent were dropouts, and one patient was a high school student. This difference was not significant.

*Previous psychiatric history.* Seventy-six percent of the comparison group had no previous psychiatric history (see Table 4). Sixteen percent had been in outpatient treatment and eight percent had been inpatients. This is not significantly different from the 44 percent of the inpatient group who had had previous psychiatric care.

**Table 4.—PAST PSYCHIATRIC HISTORY**

| | Inpatients | | Comparison Subjects | |
|---|---|---|---|---|
| Treatment | Number | Percent | Number | Percent |
| Outpatient | 8 | 32 | 4 | 16 |
| Inpatient | 3 | 12 | 2 | 8 |
| None | 13 | 52 | 19 | 76 |
| No data | 1 | 4 | 0 | |
| Total | 25 | 100 | 25 | 100 |

*Drug history.* Half of the inpatient group were taking only LSD at the time of admission and the other half were taking both LSD and marihuana or LSD and other drugs, in approximately equal numbers (see Table 5). The comparison group was taking either LSD alone (44 percent or LSD and marihuana (56 percent). It was part of the "Disciples" religion not to take other drugs.

As for past drug history prior to six weeks before being seen in the emergency room, 40 percent of the inpatient group had taken only psychedelics. Twenty percent of the inpatient group had taken multiple drugs excluding heroin, while 20 percent had used multiple drugs including heroin. Thus 40 percent were chronic multiple drug users. Twenty percent had never used any drugs in the remote past. In the comparison group in the remote past (before joining the "Disciples") 32 percent had taken only psychedelics, 44 percent were multiple drug users excluding heroin, and 24 percent were multiple drug users including heroin. Thus 68 percent were chronic multiple drug users. It should be noted that none of these differences was statistically significant.

*Diagnosis.* As recorded in the hospital charts, the resident psychiatrists diagnosed 40 percent of the inpatients as psychotic and 28 percent as neurotic; diagnoses of character disorder, borderline psychotic, and multiple diagnoses accounted for eight percent each (see Table 6). Four percent each were diagnosed as addict and adolescent adjustment reactions. We compared these diagnostic frequencies with a random sample of 95 other inpatients in the same hospital. The differences in frequency were

**Table 5.—DRUG HISTORY**

| Drug Used | Inpatients Number | Inpatients Percent | Comparison Subjects Number | Comparison Subjects Percent |
|---|---|---|---|---|
| Current history | | | | |
| Marihuana + LSD | 7 | 28 | 14 | 56 |
| LSD only | 12 | 48 | 11 | 44 |
| Other | 6 | 24 | 0 | |
| Total | 25 | 100 | 25 | 100 |
| Past drug history | (Over 6 weeks before seen) | | (Before joining Disciples) | |
| Only psychedelics (marihuana, LSD, mescaline, psilocybin) | 10 | 40 | 8 | 32 |
| Multiple * (excluding heroin) | 5 | 20 | 11 | 44 |
| Multiple * (including heroin) | 5 | 20 | 6 | 24 |
| None | 5 | 20 | | |
| Total | 25 | 100 | 25 | 100 |

* More than one of amphetamines, barbiturates, alcohol, psychedelics, and tranquilizers.

**Table 6.—DIAGNOSIS**

| Diagnosis | Inpatients* Number | Inpatients* Percent | Inpatients** Number | Inpatients** Percent | Comparison Subjects** Number | Comparison Subjects** Percent |
|---|---|---|---|---|---|---|
| Psychotic | | | 3 | 12 | 1 | 4 |
| Toxic (organic) | 2 | 8 | | | | |
| Functional | 8 | 32 | | | | |
| Neurotic | 7 | 28 | 1 | 4 | 0 | |
| Character disorder | 2 | 8 | 6 | 24 | 12 | 48 |
| Borderline psychotic | 2 | 8 | 6 | 24 | 4 | 16 |
| Addict | 1 | 4 | | | 0 | |
| Adolescent adjustment reaction | 1 | 4 | | | 0 | |
| Multiple diagnoses | 2 | 8 | 6 | 24 | 3 | 12 |
| Invalid (extreme F) | | | 3 | 12 | | |
| Undiagnosable | | | | | 5 | 20 |
| Total | 25 | 100 | 25 | 100 | 25 | 100 |

* Diagnosis via hospital chart.
** Diagnosis by MMPI testing.

small and appeared to be random; greater differences would occur by chance seven times in ten.

No attempt was made to classify the comparison group diagnostically since so many were functioning without symptoms, were not in psychiatric treatment, and were working at the time they were seen. Their indices of psychosocial disturbance were: previous school trouble (28 percent dropped out of high school), police trouble (64 percent), past psychiatric history (24 percent had had previous outpatient or inpatient care), and past history of symptoms (one person admitted to hallucinations while on LSD and another person had had anxiety symptoms prior to but not after taking LSD). Eighty percent of the group claimed to have extrasensory perception when under LSD, but this was considered to be a part of their religious beliefs and not truly delusional.

We did, however, assess psychopathology on the mental status examination (for the comparison group) and by the MMPI (for both groups). On mental status examination two comparison subjects showed a clinical concreteness in their interpretations of proverbs and one subject could not subtract sevens or threes serially. The latter subject subsequently volunteered that he had been "out of my head with pot" at the time of the examination and then did the subtractions correctly.

One of the subjects who was unable to abstract stated that he often could not think straight since he had begun to take LSD, but he had held his job as mechanic for 18 months without difficulty. He had never seen a psychiatrist, but had been addicted to barbiturates and dextroamphetamine sulfate in the remote past and had been arrested several years previously for drunk driving. His MMPI revealed a definite personality disorder associated with passive-aggressive, antisocial, paranoid, and sexually deviant trends.

The other comparison subject who was unable to abstract proverbs was a 24-year-old married father of two who had no previous psychiatric history. He had been on marihuana, barbiturates, and dextroamphetamine sulfate before joining the religious group two months prior to the initial interviewing. He had a drug and theft police record and claimed to have had trouble talking (stammering) which was cured by LSD. He had used LSD approximately 40 times in reported doses of up to 900 $\mu$g. Before he joined the group, LSD had caused "the past to come rushing forth," and occasionally "suspicious thoughts," but this was never true after joining the group.

About ten months after the initial interview one of us (J.T.U.) reveived a call from this man's wife. She stated that he had been using LSD almost every day for several months, and that she had just signed papers to have him committed to the hospital. However, he was refusing to talk to anyone but the senior author, and the judge had acquiesced. His wife stated that he had quit his job and often stayed away from home, wandering about in the woods for days at a time. He refused to eat anything colored red and threw out everything red in their house, and he frequently told her to shut up while he conversed with Jesus and the saints. The final "straw" for her was when he refused to pick up the unemployment checks.

When interviewed, he detailed his plans for beginning a new church. He spoke about green vapors interchanging from his body into the atmosphere through the umbilicus and leaned forward to whisper, "You wouldn't eat anything red, would you?" He denied having any problems, however, and claimed total happiness.

Another MMPI was obtained and compared with that from the previous year's comparison group testing. His initial MMPI (presymptomatic) showed a paranoid personality pattern. The second testing yielded a very similar profile with even more guardedness, denial, and evasiveness.

A comparison of the MMPIs on both groups revealed:

1. Most of the comparison subjects were quite defensive toward the MMPI (two-thirds at least moderately so), and they did not exaggerate or "fake sick." The inpatients did overstate; three profiles were clearly invalid, and several others were borderline. Only one inpatient was notably defensive.

2. Pd (psychopathic deviate) was the predominant peak in the comparison group and Sc (schizophrenia) was the most frequent peak of the hospitalized group (see Figure 1). All 25 inpatients had one or more deviant scores (elevations at or over a T score of 70). In contrast, only 11 of the 25 comparison subjects had one or more pathological scores. Eight men among the comparison cases and none of the inpatients had the specific sexual deviation pattern (Code 45 or Code 54).

3. A majority of the inpatients obtained mixed, borderline, and overtly psychotic patterns; only five of the 25 comparison subjects appeared borderline psychotic on the testing, although a few others were ambiguously defensive. However, none of these five were openly schizoid patterns; rather, all were of a controlled and potentially paranoid type.

4. The comparison subjects obtained character disorder types of patterns quite consistently, but many of these were well within the normal range. Although character disorder elements occurred consistently in the profiles of the inpatients, they were complex, mixed, and predominantly psychotic patterns.

To summarize our results, the inpatient and comparison groups did not show significant differences in race, sex, age, education, or early parental deprivation. Significant differences were found in marital status, occupational history, and police records. Severe psychopathology was seen clinically in the inpatient group while hospitalized. No comparable clinical psychopathology was evident in the comparison sample. The MMPI profiles clearly corresponded to these results, although the comparison group was much more defensive toward the testing. (MMPI profiles are shown in Figure 1.)

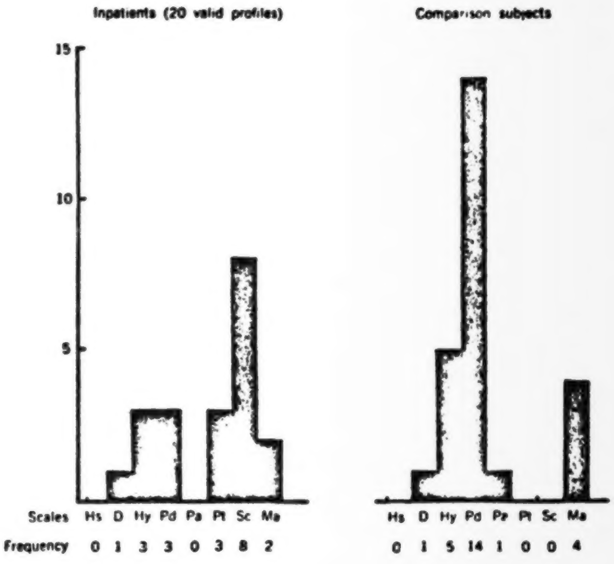

Figure 1.—*Frequency of Highest Elevations Among the Two Groups on the Eight Basic Clinical Scales of the MMPI (Hypochondriasis, Depression, Hysteria, Psychopathic Deviate, Paranoia, Psychasthenia, Schizophrenia, and Hypomania)*

## Discussion

It can be asked whether all those who had chronic adverse LSD reactions were emotionally predisposed or were to some degree emotionally ill prior to LSD ingestion. This is very difficult to answer. Well known at many hospitals are the anecdotal reports of local interns and residents who were carefully screened before taking LSD (or had even been psychoanalyzed) but who subsequently had severe adverse reactions from LSD. In addition there are now a number of reports of nonprofessional persons screened by psychiatric history and/or psychological testing who have had adverse LSD reactions. Although 44 percent of our inpatients with a history of previous psychiatric care is a high figure, it is certainly less than 100 percent. None of the 24 percent of the comparison group who had previous psychiatric treatment had difficulty from their ingestion of LSD.

Among psychiatric patients with LSD histories, we are now seeing at the hospital fewer chronic, multiple drug users who are obviously emotionally disturbed. Instead we are seeing more teenagers who tried LSD once, for example at a party, got over its effects in 12 to 16 hours, but then presented at a hospital some months later with recurrent symptomatology without ever having taken the drug again. A decreasing proportion of our patients are chronic drug users. However, it is not clearly demonstrable whether this is due to a change in incidence or to a shift in selective referrals to our hospital.

This brings us to a consideration of set or, specifically, the attitude with which one approaches the LSD experience and the setting or environment in which one takes the LSD. Everyone recognizes the importance of these factors in the LSD experience. In fact people now have "psychedelic experiences" in groups in the proper setting where they hallucinate, etc., but *never* take drugs at all (5).

The parallels between the LSD subject and the good hypnotic subject are striking, particularly in the realm of passivity and suggestibility. Our comparison group dressed alike and even used identical phrases in answering questions. One of their favorites was "for sure," chanted over and over. They obviously received a tremendous amount of support, both during and between trips, from the group itself. The average length of stay with the group was eight months, and 24 of the 25 controls claimed that LSD (taken with the group) had led them to "God, love, or peace of mind." They may thus have been successful LSD users because the group support outweighed or overcame the adverse potentials of the drug.

We should not conclude, however, that set and settings are the only determinants of the type of trip one has. There is one study reported where all subjects expected psychosis, but all felt only relaxed and friendly after LSD (1). There is an ever-growing LSD mythology, too, much of it having to do with set and setting (6, 7). For example, one commonly hears that a bad LSD experience will not result if:

—One is in a calm frame of mind (no fights that day with spouse or employer);

—One takes the LSD with one or two good friends or with an experienced sitter or guide present;

—The room has soft lighting and a thick carpet or mattress to sit on;

—One is listening to the Indian music of Ravi Shankar and reading reassuring phrases from the *Tibetan Book of the Dead;* and perhaps if one has a "downer" or chlorpromazine pill at hand.

But we have hospitalized many persons who had taken these precautions and who also had had up to 100 previous good LSD experiences. Our inpatient group took their LSD in many varied settings, from kick-type, acid-test parties (56 percent) to isolated ingestions in their rooms (16 percent). However, some (8 percent) were most careful and serious about the preparations for taking LSD. (There were no data for setting in 20 percent of the inpatient group.) Despite their hospitalizations a large proportion of the inpatients persisted in claiming benefit from the drug and many returned to it after discharge.

How reliable were the data from our comparison group? Obviously they were proselytizers of LSD. This could explain why they all claimed no previous religion and even no religion for their parents. It also could explain why they claimed to have developed "ESP" as well as to have found love from LSD and also why they identified themselves as a "bunch of ex-criminals and drug addicts" before using the drug.

## Summary

Twenty-five hospitalized psychiatric patients with adverse LSD reactions were compared to a sample of 25 subjects who had not had adverse reactions from the repeated use of LSD.

In all of our comparisons there were no historical elements or current clinical aspects that were unique to either group. Clearly there is no single factor that guarantees immunity from an adverse LSD reaction. The prediction of successful versus unsuccessful users is further complicated by the occurrence of cases in which subjects used LSD 100 times or more with no adverse reactions and then subsequently developed psychiatric symptomatology. Set and setting appear to help but not to guarantee against adverse complications.

One hypothesis, strongly supported by our test data, is that the LSD interacts with schizoid trends, unsteady reality testing, and related psychological factors. Such a complex interaction—which is difficult to anticipate even with the best of clinical and test data—would predict that adverse LSD reactions will be with us for some time to come.

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# Persons with Exceptionally High Risk of Leukemia

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## Summary

Epidemiologic research has helped to identify 5 classes of persons whose probability of developing leukemia within a relatively short time is 1 in 100 or greater. Common to all is a distinctive genetic or cytogenetic characteristic, either inherited or acquired. These observations suggest studies to identify additional high-risk groups and to clarify the role of genetics in leukemogenesis.

## Introduction

Epidemiology has helped to clarify the origins of leukemia (*a*) by testing hypotheses developed through laboratory experimentation and (*b*) by generating hypotheses through descriptive studies and the identification of persons at exceptionally high risk of the disease. My present purpose is not to review comprehensively information we have published elsewhere (12, 19, 20), but to examine recent developments concerning high-risk groups to evaluate how they relate to one another and to future epidemiologic research on leukemogenesis.

The advantage in identifying groups of persons especially prone to a disease is that one can seek among them features in common which may be of etiologic significance. In the past decade a variety of circumstances have been defined which carry a high risk—1 in 100 or greater—of developing leukemia within a relatively short time. This information is summarized in Table 1.

## Identical Twins

At the greatest risk thus far known is the child whose identical twin has developed leukemia. The probability is about 1 in 5 that he will develop the disease usually within weeks or months after his twin falls ill (17). There is no such risk among fraternal twins. This finding has not been confirmed in England and Wales (14), but additional cases have been observed in the U. S. (R. W. Miller, unpublished observations). The near-simultaneous onset of the disease among both members of the twin-pair adds to the belief that these occurrences are not due to chance. The evidence to data suggests that the risk among identical twins may not extend beyond 7 years of age. This point will be clarified when the 15,500 male twins who served in the U. S. Army during World War II have been classified as to probable zygosity (15), and a determination made of the concordance rates for leukemia. It is, of course, important to continue to seek confirmation here and abroad for the previously reported concordance rate of about 20% for leukemia among identical twins in childhood. Additional data in the U. S. will be sought through a recently established national registry of birth and death certificates for all children who have died of cancer since 1960.

Recognition of the extraordinary risk of leukemia in the young child whose identical twin has developed the disease provides investigators with the opportunity to study the as yet unaffected twin in regard to cell kinetics, immunity, virologic status, and chromosomes with the expectation that, on the average, in one out of five instances the child will develop the disease within a short time. Retrospective investigations may reveal why 80% of co-twins escape the disease, although both members of a pair are genetically identical and share the same environment.

### Inherited Tendency to Chromosomal Breakage

Bloom's syndrome inherited through an autosomal recessive gene, is characterized by photosensitive telangiectasia of the face and an unusual susceptibility to acute leukemia. Though the data are as yet scarce, they suggest that 1 in 8 persons with the syndrome will develop leukemia over the first 30 years of life [3 leukemics among 23 persons with the syndrome (26)]. In Bloom's syndrome there is excessive chromosomal breakage and rearrangement on cell culture, a trait shared with Fanconi's aplastic anemia and ataxia-telangiectasia, inherited disorders which also apparently predispose to acute leukemia (5, 13). As experience with these congenital defects increases and as diagnoses are made earlier in life, a more accurate estimate of leukemia occurrence will be obtained. Should excessive chromosomal breakage be recognized in other genetically induced diseases, study of affected persons and their families for the occurrence of leukemia will be informative.

### Acquired Chromosomal Breaks

Chromosomal breaks can be produced by a variety of agents to which man is exposed (4, 9, 24, 30), and 2 of these, ionizing radiation and benzene, have been implicated in human leukemogenesis. Observations on the Japanese survivors of the atomic bombs provide convincing evidence that whole-body radiation in sufficient dosage is leukemogenic in man (3). Study of patients given radiotherapy for ankylosing spondylitis indicates that partial-body exposures may also induce leukemia (10). In both studies, the frequency of the neoplasm was proportionate to the radiation dose, and the peak incidence occurred about 6 years after exposure. In the spondylitis study the elevation in leukemia rate disappeared 15 years after X-ray therapy, but among the atomic-bomb survivors it was still elevated when last reported, twenty years after exposure (3). In both studies, acute leukemias and chronic granulocytic leukemia were induced by radiation, but chronic lymphocytic leukemia was not. In neither study could it be determined whether there was a radiation dose below which no leukemia was induced; the sample size, large as it was, was still too small to evaluate an effect below about 80 rads (7). Further observations are required to determine how long the rates among the atomic-bomb survivors remain elevated, and whether the rates in either study will rise again as the latent period lengthens or as environmental circumstances change. Time will tell also if chronic lymphocytic leukemia is a long delayed sequel of radiation exposure.

It should be noted that the risk of leukemia following heavy exposure to the atomic bomb (within 1000 meters of the hypocenter) was about 1 in 60 over 12 years, substantially less than that in Bloom's syndrome or for the child whose identical twin has developed leukemia.

The marked predisposition to leukemia in polycythemia vera (16% of patients treated with X-ray, $^{32}P$ or both) has been attributed by Modan and Lilienfeld (22) to a radiation effect, since leukemia developed in only 1.6% of patients who were not treated with radiation. Kay *et al.* (16), however, have since described aneuploidy in 7 of 11 cases before treatment, a circumstance which may contribute to leukemogenesis. It should be noted that, as shown in Table 1, the frequency of leukemia in radiation-treated polycythemia vera (1 in 6) was substantially higher than it was among persons heavily exposed to the atomic bombs in Hiroshima (1 in 60) or among British patients given X-ray treatment for ankylosing spondylitis (1 in 270). The implication is that persons with polycythemia vera are much more prone than usual to the leukemogenic effect of ionizing radiation.

Table 1.—GROUPS AT EXCEPTIONALLY HIGH RISK OF LEUKEMIA

| Group | Approximate risk | Time interval | References |
|---|---|---|---|
| Identical twins of children with leukemia | 1 in 5[a] | Weeks or months | MacMahon and Levy (17) |
| Radiation-treated polycythemia vera | 1 in 6 | 10–15 years | Modan and Lilienfeld (22) |
| Bloom's syndrome | 1 in 8[b] | $<$30 years of age | Sawitsky *et al.* (26) |
| Hiroshima survivors who were within 1000 meters of the hypocenter | 1 in 60 | 12 years | Brill *et al.* (7) |
| Down's syndrome | 1 in 95 | $<$10 years of age | Barber and Spiers (2) |
| Radiation-treated patients with ankylosing spondylitis | 1 in 270 | 15 years | Court Brown and Doll (10) |
| Sibs of leukemic children | 1 in 720 | 10 years | Miller (18); Stewart (29) |
| U. S. Caucasian children $<$ 15 years of age | 1 in 2880 | 10 years | U. S. Vital Statistics (23) |

[a] Of 22 identical twins with leukemia, the co-twin was affected in 5 instances.
[b] Three leukemics among 23 persons with Bloom's syndrome.

The evidence that benzene is leukemogenic in man depends largely on an occupational cluster of cases among Italian shoe workers who used benzene in their trade (31). It remains for some investigator with access to workers heavily exposed to this chemical to conduct a prospective study to estimate the magnitude of the risk.

In the search for other leukemogens, attention should be directed to agents, chemical or viral, which produce chromosomal breaks. A prime suspect at present is lysergic acid diethylamide (LSD-25), which has been widely used for its hallucinatory effects. It induces long-lasting chromosomal abnormalities ("quadriradials") which characterize Bloom's syndrome and Fanconi's aplastic anemia (8). It will be of interest to study the frequency of leukemia not only among adults who have taken LSD-25, but also among children exposed *in utero* when their mothers took the drug.

### Extra Chromosomes

The risk of leukemia is increased not only in certain conditions with excessive chromosomal breakage, inherited or acquired, but also in Down's syndrome (2), which typically has an extra chromosome in the G group. Whether persons with other congenital aneuploidy are also prone to this neoplasm is as yet uncertain. An accumulation of case reports suggests that Klinefelter's syndrome, in which there is an XXY sex-chromosome complement, predisposes to leukemia (12). Conclusive evidence of a relationship between the two diseases awaits (*a*) the results of a prospective study by Court Brown *et al.* (11) based on a registry of persons with abnormalities of the sex chromosome complement, or (*b*) the demonstration of an excess of Klinefelter's syndrome among persons with leukemia. Another form of congenital aneuploidy, D-trisomy, rare as it is, has been described with leukemia in 2 instances despite the short life-span of infants with the syndrome (27, 32).

These observations suggest that cytogenetic study of leukemic children in remission might reveal an excess frequency of chromosomal abnormalities. Among 25 leukemic children so studied, Borges *et al.* (6) found 3 with congenital aneuploidy on examination of the skin and blood: XXY, probable XYY, and F-trisomy. The study is being extended to obtain a more precise estimate of the frequency and variety of chromosomal aberrations present before the onset of leukemia.

Case histories indicate that congenital chromosomal aneuploidy and leukemia may aggregate more often among sibs than can be attributed to chance (21). Definitive evidence through epidemiologic study is difficult to achieve because of the large sample size required to demonstrate an excess of such clusters even if the frequency were several times greater than normal expectation.

### Sibs of Leukemic Children

Two published reports (18, 29) leave little doubt that aggregation of childhood leukemia in sibships can be demonstrated when the sample size is large enough (1000 or more sibs). The excess over normal expectation is about fourfold. Other investigators have described 2 families in which aggregation of leukemia or a leukemia-like disease was genetically influenced: ataxia-telangiectasia with acute lymphocytic leukemia in 2 sibs (13), and a myeloproliferative disorder simulating myelogenous leukemia among four sets of sibs in a kindred (25). It is to be expected that acute leukemia may also aggregate among sibs in families with other heritable leukemia-prone disorders: Bloom's syndrome, Fanconi's aplastic anemia or congenital (X-linked) agammaglobulinemia. These possibilities indicate that, when leukemia is found in sibs, the family be studied cytogenetically and immunologically for the characteristic abnormalities of the known inherited diseases which predispose to leukemia. It would also be of value to determine if the morphology or natural history of leukemia in these families differs from usual.

The association of acute leukemia with the diseases mentioned above apparently is influenced by the action of rare recessive genes. The role of inheritance may be further defined by study of a series of cases in Japan with respect to the frequency of parental consanguinity. An inbreeding effect would be revealed if cousin marriages had occurred more often than usual among the parents of leukemic persons [about 4% of the marriages in Japan involve first cousins (28)]. The elevated concordance rate for leukemia in identical twins under 7 years of age (17) suggests that leukemia early in life may in particular reveal a consanguinity effect.

Table 2.—DISTINCTIVE GENETIC FEATURES OF GROUPS AT HIGH RISK OF LEUKEMIA

| High-risk category | Genetic feature |
|---|---|
| Identical twin of child with leukemia | Genetically identical |
| Bloom's and Fanconi's syndromes | Genetically induced chromosomal fragility |
| Radiation-treated polycythemia | Aneuploidy prior to radiation; chromosomal breaks subsequently |
| Exposure to ionizing radiation or benzene | Long persisting chromosomal breaks |
| Down's syndrome | Congenital aneuploidy |

### Perspective

There is a surprising diversity of cytogenetic findings among groups at high risk of leukemia. Yet, as shown in Table 2, there is a common denominator in that each high-risk group has a distinctive genetic or chromosomal feature which may well play a role in leukemogenesis.

Though certain viruses alter chromosomes, induce leukemia in experimental animals, and cause human tissue culture to undergo malignant transformation (1), no virus has yet been implicated in the genesis of human leukemia. A large array of epidemiologic tests have failed to show that the disease is transmitted from one person to another in either a vertical or horizontal fashion which suggests an infectious spread (19). The negative epidemiologic results to date do not disprove the viral origin of leukemia, for subtlety in the mode of transmission may defy present technics to reveal it.

It is noteworthy that diseases or environmental agents which predispose to leukemia do not also predispose to lymphoma (12). On the other hand, genetically induced disorders characterized by severe immunologic deficiency carry a high risk of lymphoma and probably of acute lymphocytic leukemia, but, so far as we know, there is no predisposition to granulocytic leukemia. These observations indicate that in etiologic studies it is desirable to separate the various forms of leukemia from one another and from solid tumors of the lymphoid system.

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# Chromosomal Damage in Human Leukocytes Induced by Lysergic Acid Diethylamide

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Abstract. *Addition of lysergic acid diethylamide to cultured human leukocytes resulted in a marked increase of chromosomal abnormalities. The distribution of chromosome breaks deviated significantly from random, with an accumulation of aberrations in chromosome No. 1. Cytogenetic investigation of a patient extensively treated with this drug over a 4-year period for paranoid schizophrenia showed a similar increase in chromosomal damage.*

The induction of chromosomal abnormalities by various exogenous agents has been studied extensively (1, 2). In addition, compounds with specific pharmacologic and chemotherapeutic value cause chromosome damage (3). The psychotomimetic agent lysergic acid diethylamide (LSD–25), when added to cultures of human peripheral leukocytes, produces a marked increase in the frequencies of chromosomal breaks and rearrangements compared to untreated cultures.

Chromosomal preparations were made from cultures of whole blood with a microtechnique and standard procedures (4). All cultures were incubated for 72 hours at 37°C, and colcemide (0.05 $\mu$g/ml) was added for the last 2 hours of culture to arrest cells at metaphase. Lysergic acid diethylamide was dissolved in sterile distilled water and added to the cultures in various concentrations (100, 50, 10, 1, 0.1, 0.01, and 0.001 $\mu$g/ml of culture) for different periods of exposure before harvest (48, 24, and 4 hours). Concentrations of 100 and 50 $\mu$g/ml caused cellular degeneration and suppressed mitosis so that the number of analyzable cells was insufficient. Leukocytes obtained from two healthy individuals (one male and one female) were treated with LSD–25 at final concentrations of 10, 1, 0.1, 0.01, 0.001 $\mu$g/ml for 48, 24, and 4 hours. Each concentration and exposure time was repeated twice. The controls consisted of untreated cultures from these two individuals as well as from four additional persons, two males and two females.

Several slides from each culture were prepared and coded by individuals who did not participate in the microscopic scoring of the cells. It was hoped that 25 metaphases per slide could be obtained to yield a total of 200 cells for each concentration and time period. However, in some of the treated cultures, we could not find this number of cells. Well-spread mitoses were selected under low magnification (× 250), and chromosomes were scored under oil-immersion phase-contrast microscopy (approximately × 1560). Once a cell was selected under low power, it was included in the study.

Abnormalities were scored as breaks only if a clear discontinuity of the chromatid was visible. Breaks were classified as "chromatid" if only one chromatid was affected and "isochromatid" if both sister chromatids were broken at the same location. Both of these types of abnormalities were scored as single breaks. Single fragments were included with chromatid breaks while "double" fragments were scored as isochromatid breaks. Dicentric chromosomes and "translocation" configurations were considered as containing two breaks. Attenuated, pale-staining chromosomal regions, other than the normal secondary constrictions, were scored separately as "gaps" but were not included in the calculation of breakage rates. Whenever possible, each break was assigned to a given identifiable chromosome or chromosome group according to the Denver classification (5).

Since there was no observable difference in the responses of the two individuals, the data for each treatment were pooled. Table 1 illustrates the distribution of chromosomal abnormalities observed for various exposure times and concentrations of the drug. At least a twofold increase in the rate of chromosomal breaks over the control rate was evident for all treatments (except 0.001 μg/ml for 4 hours). A relationship between dose and response existed; however, this appeared to be time dependent. The highest concentration (10 μg/ml) caused greater damage in shorter incubation times, an indication that the longer exposure may have caused cellular destruction. The same effect is also noted with a concentration of 1.0 μg/ml in the 48-hour treatment. Conversely, with 0.001 μg/ml, more chromosomal damage was evident at longer exposure times, while, with the 4-hour exposure with this dosage, a direct reduction in the number of chromosome breaks was observed.

Table 1.—DISTRIBUTION OF CHROMOSOMAL BREAKS INDUCED IN CULTURED HUMAN LEUKOCYTES BY VARIOUS DOSAGES OF AND TIMES OF EXPOSURE TO LSD–25. DATA ARE GIVEN AS BREAKS PER NUMBER OF CELLS. FIGURES IN PARENTHESES DENOTE BREAKS PER CELL.

| Time before harvest (hours) | Dosage (μg/ml) | | | | |
|---|---|---|---|---|---|
| | 10 | 1 | 0.1 | 0.01 | 0.001 |
| 48 | 15/164<br>(0.091) | 13/194<br>(0.067) | 41/125<br>(0.328) | 19/200<br>(0.095) | 27/195<br>(0.138) |
| 24 | 22/200<br>(0.110) | 46/125<br>(0.368) | 34/175<br>(0.194) | 28/175<br>(0.160) | 22/175<br>(0.216) |
| 4 | 38/150<br>(0.253) | 18/200<br>(0.090) | 23/200<br>(0.115) | 28/200<br>(0.140) | 10/200<br>(0.050) |
| Control | 34/925 = (0.037) | | | | |

Table 2.—DISTRIBUTION OF CHROMOSOME BREAKS ACCORDING TO INDIVIDUALLY IDENTIFIABLE CHROMOSOMES OR CHROMOSOME GROUPS. THERE WERE 30 UNIDENTIFIABLE FRAGMENTS AND BREAKS. DATA ARE GIVEN AS NUMBERS OF BREAKS.

| Distribution by chromosome group | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| A1 | A2 | A3 | B | C | D | E | F | G | |
| | | | | *Observed* | | | | | |
| 74 | 28 | 18 | 33 | 161 | 15 | 16 | 7 | 2 | 354 |
| | | | | *Expected* | | | | | |
| 30.8 | 28.8 | 24.1 | 43.0 | 131.9 | 35.6 | 30.6 | 16.1 | 13.1 | 354.0 |
| | | | | *Chi-square test** | | | | | |
| 60.6 | | 1.5 | 2.3 | 6.4 | 11.9 | 7.0 | 5.1 | 9.4 | 104.2 |

* d.f. = 8; $P < .001$.

Table 2 depicts the distribution of chromosome breaks among the various identifiable chromosomes or chromosome groups. The test of significance indicates a nonrandom distribution of breaks ($P < 0.001$), with a disproportionate accumulation of anomalies in chromosome No. 1. The array of expected values is based on random breakage per unit of chromatin as calculated from the Denver measurements (5). Studies of other agents inducing nonrandom breakage of human chromosomes have demonstrated "hot spots" in the heterochromatic regions of chromosome No. 1 [for example, the centromere and secondary constriction (2)]. Lysergic acid diethylamide also shows an apparent affinity for these chromosomal regions.

At most concentrations, the greatest damage was induced by 24- and 48-hour exposure periods. Although the leukocyte system is not an absolutely synchronized cell population, a large proportion of the cells seen at metaphase after 72 hours of culture must have been in either the $G_1$ (before DNA synthesis) or S (DNA synthesis) period during these longer exposure times, while 4 hours before harvest the cells are in the $G_2$ period (after DNA synthesis) of the cell cycle. Since in most cases the lowest frequency of breaks was observed after this 4-hour exposure (except where the dose was 10 μg/ml), LSD–25 may cause chromosome breaks during the $G_1$ or S period of the cell cycle. Figure 1, a–d, illustrates typical chromosomal aberrations observed in vitro.

We also studied the leukocytes of one patient who had undergone extensive treatment with LSD–25 in conjunction with psychotherapy for paranoid schizophrenia. This patient is a 51-year-old male who, with the exception of his schizophrenia, is physically healthy with no history of malignancy, viral infection, or radiation treatment other than routine diagnostic procedures. From 30 September 1960 to 9 March 1966 he had a total of 15 treatments with LSD–25. The ingested dosages were 80, 100 (three times), 150, and 175 μg for the first six treatments, while the last nine treatments were

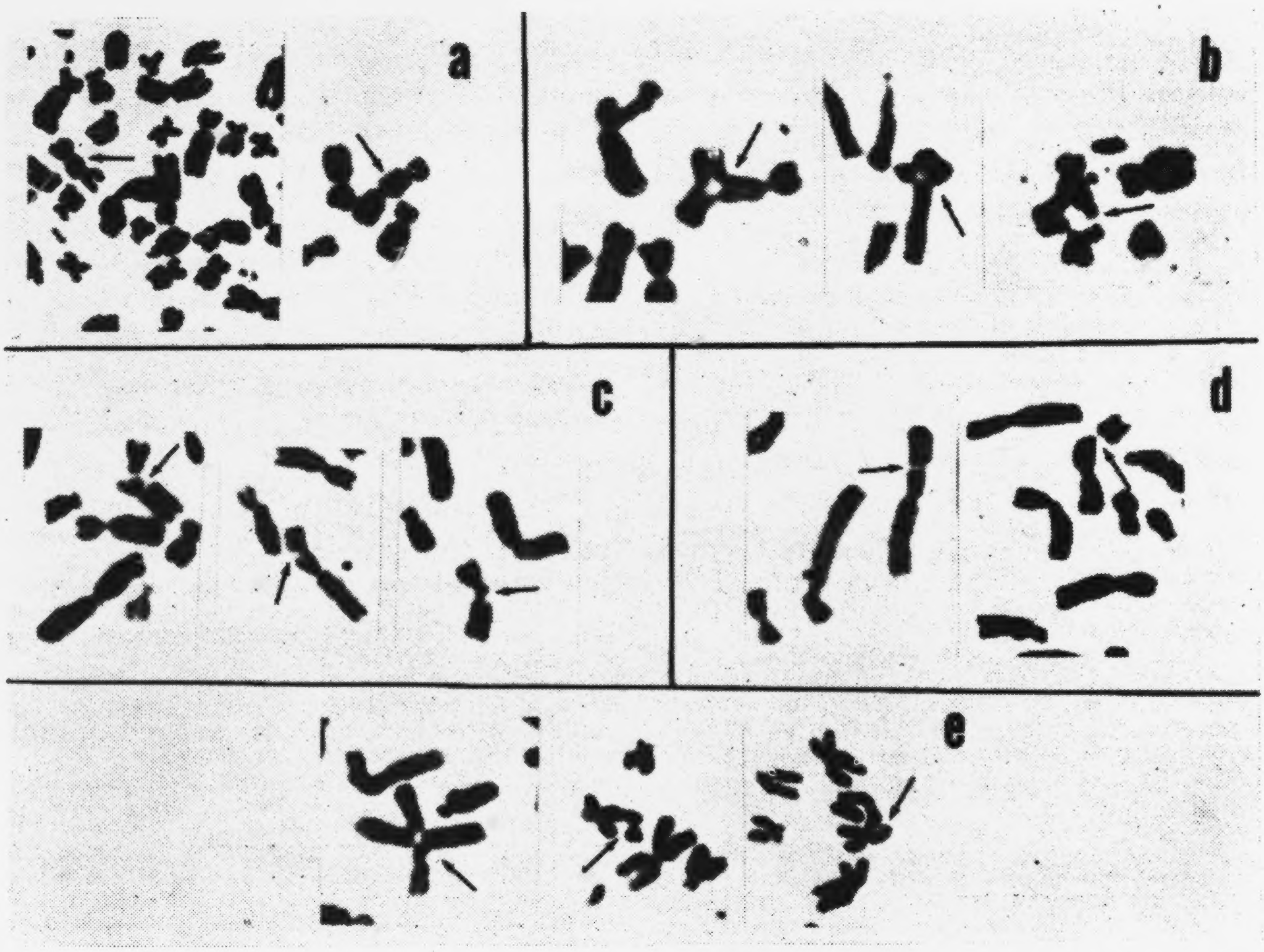

Figure 1.—*Partial cells with various chromosomal abnormalities induced by LSD–25 (approximately × 2400). (a) Arrows indicate dicentric chromosomes seen in two cells. In the cell on left notice two double fragments and one single fragment. (b) Chromatid exchanges from three different cells. (c) Single chromatid breaks. (d) Isochromatid breaks. (e) Chromosomal anomalies in leukocytes of the patient treated with LSD–25 (quadriradial and two chromatid breaks).*

with 200 μg. Leukocyte cultures were initiated for chromosomal preparations 8 months after the last treatment. There was no other known ingestion of drugs of any kind during this interval. The chromosome breakage rate of 200 cells in metaphase was 12 percent compared to the normal 3.7 percent. Figure 1e demonstrates some of the chromosomal anomalies seen in the patient. Of extreme interest is the one quadriradial formation observed between two No. 1 chromosomes. Such figures are seen in only extremely low frequencies in untreated, normal cultures but may be induced routinely by treatment of human leukocytes with mitomycin C (6). The genetic consequences of this phenomenon have been discussed (7). "Quadriradials" and increased chromosomal breakage also characterize the cytogenetic picture in two syndromes—Bloom's syndrome and Fanconi's anemia—caused by autosomal recessive genes (8). Such exchange figures also are frequently observed in tumor cells as well as cells that have undergone "malignant transformation" by the oncogenic virus $SV_{40}$ (9). It is also of interest that patients with Bloom's syndrome and Fanconi's anemia demonstrate an increased frequency of developing neoplasia (10).

Since the patient we studied had been treated for short periods of time with the tranquilizing drugs chlorpromazine (thorazine) and chlordiazepoxide (librium) before and during treatment with LSD, our cytological findings should be interpreted with caution. However, screening of chromosomes from 35 schizophrenic patients, some of whom were treated with these tranquilizers in a double-blind study, revealed no increase in the frequency of chromosome breakage over that in untreated individuals (11).

The significance of these findings cannot yet be assessed fully. However, LSD-25 is apparently another agent which is capable of quickly producing chromosomal damage in vitro, perhaps in the first or second division of cultured leukocytes. Moreover, the observation of increased chromosomal damage in the patient suggests an additional long-term effect of the drug. Individuals accidentally exposed to irradiation (12), therapeutically irradiated (13), or treated with the chemotherapeutic agent 1, 3-bis (2-chloroethyl)-1-nitrosourea (14) and then studied long after the initial exposure still manifest increased frequencies of chromosomal abnormalities. Such studies suggest two possible mechanisms of LSD action: (i) permanent damage to the stem cells that may give rise to subsequent leukocytes, or (ii) damage in the $G_1$ period to long-lived lymphocytes, the damage not being observed as chromosomal abnormalities until mitosis. The latter may be the more likely hypothesis.

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# Therapeutic Effects of LSD: A Follow-up Study

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Lysergic acid diethylamide (LSD) has been used to treat many psychiatric patients, but its status as a therapeutic agent remains uncertain and controversial. Specific indications for therapy with LSD have not been established, although there is some evidence that patients with conduct disturbances, *e.g.*, chronic alcoholics and sexual deviates, tend to respond favorably even to limited treatment (3, 4). The present investigation was carried out in an attempt to define some indications for LSD therapy and to develop prognostic indicators. The study was divided into two phases: the first focused on the relationship between insightful experience produced by LSD and swift clinical improvement; the second extended the study to evaluate the stability of this improvement by studying the patients a year after LSD treatment.

Results of the first phase have been reported previously by Eggert and Shagass (6). This aspect of the study was designed to test the assumption that patients who react to LSD with an insightful response are more likely to show favorable behavioral change than those who do not. One aim was to determine clinical criteria predictive of insightful response. Other authors have used terms such as "mystical," "cosmic," "psychedelic" and "consciousness-expanding" to designate the insightful response (7, 8). For the purposes of this study an insightful response occurred if, during an LSD session, the patient experienced early memories and altered his perception of his relationships to the world; if he related these memories and fresh perceptions to his present problem; and if he made a convincing resolution to change his future behavior as a consequence of his new understanding.

Patients who responded to LSD therapy with insightful experiences of this kind were distinguished from those who showed no such response by raters who listened to tape recordings of the sessions. Eight patients were classified as "responders," and 12 were classified as "nonresponders."

Seven of the eight responders were found to be among nine patients who had been diagnosed as psychopathic personality because they showed five of 15 criteria for this diagnosis designated in the Small (10) structured interview. The results, demonstrated a significant relationship between psychopathic personality characteristics and a tendency to react to LSD with an insightful response. It was also found that no subject under 22 years of age was classified as a responder.

The present report deals with results from the second phase of the study, a follow-up evaluation of the same 20 patients after one year. Obviously, the prognostic value of predicting immediate insightful response to LSD depends upon the later clinical course associated with the type of immediate response. Although the answer to this question rests on comparisons of outcome in the responder and nonresponder groups, the design of the follow-up study also permitted comparison of outcome in all patients treated with LSD with that of a matched group of patients who were not given LSD.

## Methods

### SUBJECTS

Subjects were 20 psychiatric inpatients at the Psychopathic Hospital, Iowa City, Iowa. All submitted voluntarily to treatment and signed a special experimental treatment release form. A deliberate attempt was made to recruit patients with conduct disturbances. Ten subjects were court-referred or had some legal problem related to psychiatric contact. Ages ranged from 16 to 36 years (median, 24); 13 were men. Selection procedures were designed to exclude subjects with overt psychoses, mental retardation and brain syndromes. Small's (10) structured interview was used to clinically evaluate patients prior to LSD administration. All responses to standard questions were recorded verbatim on a protocol sheet; these were then used to complete a check list of diagnostic criteria, which led to classification according to predetermined rules. Although the classification system differs in some respects from that of the American Psychiatric Association, use of the Small procedure insures greater reliability because it reduces variability. By this method the patients were grouped in the following diagnostic categories: psychopathic personality, nine cases; exogenous depression, five; psychoneurotic reaction, four; schizophrenic reaction, one; no diagnosis, one. The patient diagnosed as schizophrenic reaction was not at the time obviously psychotic, although later observation verified this diagnosis. No patients received drugs for at least 48 hours before test injections; only five had taken medications for their present condition.

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This study was conducted at the Psychopathic Hospital, Iowa City, Iowa. The cooperation of the medical staff, directed by Dr. Paul E. Huston, is gratefully acknowledged. Sandoz Pharmaceuticals supplied the LSD.

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### Treatment Procedure

LSD was administered intravenously at a dose of 2.5 mg/kg body weight. In this group it was given only once. The intravenous method was used to speed the action of the drug and to reduce variability of response due to absorption differences. Preparation for the drug sessions consisted of at least six interview hours over a seven- to 14-day period. In these interviews current problems were explored and subjects were informed that the drug session could lead to unusual and important experiences. Sessions took place in the office of the investigator who administered the drug and stayed with the patient almost continuously from 9 A.M. until evening; he attempted to maintain a supportive, interested and generally nondirective attitude. At bedtime chloropromazine, 25 to 50 mg, was administered. Twelve patients also received 20 mg of methamphetamine intravenously on another day (alternate order of administration) in an attempt to compare the effects of the two drugs. However, it was found that observers could easily distinguish between LSD and methamphetamine.

### Classification of Insightful Response

Degree of insightful response to LSD was rated independently by two psychiatrists, not otherwise involved in the study, from tape-recorded samples of the LSD session totaling about 60 to 90 minutes. Ratings were on a scale from 0 to 3+. The raters had available full routine case material about each patient but not the structured interview data. A 3+ rating was assigned to sessions in which there was reliving of forgotten childhood experiences, integration of this material, and realistic self-acceptance with the resolution to improve. Ratings of the two observers were identical in 11 of 20 cases and within one point in 18 of 20. Ratings were skewed toward the zero end of the scale, but it was possible to divide the cases into those responding more and those responding less by taking a mean rating of 1.0 or more to indicate a responder.

### Follow-up Procedure

Case histories were reviewed, and a list of symptoms and deviant behavior characteristic of each LSD patient was compiled. For every patient treated with LSD the hospital records were searched to find a patient treated by means other than LSD, who would match the LSD case closely for age, sex, marital status, years of education, psychiatric diagnosis, and for his pattern of symptoms and deviant behavior. Due to the large number of hospital cases available, it was possible to achieve satisfactory matching. Two examples presented in Table 1 illustrate the similarity of clinical features in LSD and control patients. All LSD cases and their matched controls were contacted by letter; letters were also sent to significant relatives such as parents and spouse. If the letter did not elicit a response, telephone calls were placed. Appointments were then made for both the patients and their relatives to be seen and interviewed. Those who could not come to the hospital were interviewed by telephone, as were the relatives. In one instance, the whereabouts of the patient was unknown, so only his wife was interviewed. In another case, the patient was in prison, and an interview was conducted by the prison psychiatrist, who followed a prescribed interview schedule.

Each patient and relative was asked to rate changes in symptoms and deviant behavior listed for that patient at six months and 12 months following treatment with LSD, or following discharge from hospital in the group not treated with LSD. The patient and his relative were also asked to note improvement in any particular aspect of behavior. If there had been improvement, they were asked to rate its degree on a 4-point scale with steps defined as 25, 50, 75 or 100 per cent. A 100 per cent improvement was indicated if the behavior or symptom in question was no longer a problem to the individual or his family. Improvement ratings were coded on a scale from 0 to 4, and the ratings of the patient and his relative were averaged for each manifestation.

Table 1.—TWO EXAMPLES OF CASE MATCHING

| Manifestation Rated | LSD Case | Control |
|---|---|---|
| Case 1 | | |
| Dexedrine habituation | * | * |
| Overt homosexuality | * | * |
| Excessive use—other meds. | * | * |
| Poor relationship to females | * | * |
| Anxiety and depression | * | * |
| Feels sexually inadequate | * | * |
| Case 2 | | |
| Checks with insufficient funds | * | * |
| Embezzlement ($13,000) | * | |
| Extorting money from people | | * |
| Lying | * | * |
| Excessive drinking | * | * |
| Sexual promiscuity | * | * |
| Conflict with authority | * | * |
| Poor work record | * | * |
| Gambling | * | |
| Irresponsible to family | * | * |
| Feels inadequate | * | * |

* Indicates presence.

## Results

In view of the diversity of symptom and behavioral manifestations, it seemed reasonable to compare overall ratings of clinical change. The change ratings from 0 to 4 were averaged to achieve a single overall change rating at six and 12 months for each patient. Mean ratings were then compared for the LSD-treated and non-LSD-treated group and for the LSD responders and nonresponders. A summary of the follow-up results is shown in Table 2. Statistical significance was evaluated by means of *t*-test (two-tailed). It is seen that the LSD-treated group at six months was rated significantly more improved than the control group ($p < .05$). At 12 months, the LSD group still showed greater improvement ($p < .02$). Within the LSD group, those who had insightful responses during the LSD session were considered much more improved at six months than those classified as nonresponders ($p < .001$). The LSD responders were still significantly more improved than the nonresponders at 12 months ($\text{p} < .02$), but the difference was not as great.

Table 2 also shows the mean change in ratings of improvement between six and 12 months and the significance of the difference. Only the LSD nonresponders showed acceptably significant continuing improvement ($p < .01$). Clinical improvement tended to recede between six and 12 months in the LSD responder group.

The data were examined to determine whether particular behavior or symptom areas showed greater change in response to LSD; responders and nonresponders were also compared along these lines. Table 3 shows some comparisons in three behavior areas. The small number of cases precluded meaningful statistical tests on these findings. However, the LSD responders showed more improvement than any other group in the areas of sexual behavior and excessive use of alcohol or drugs. On the other hand, in ratings of school, home or job performance, the considerable improvement of the LSD responder group at six months had largely vanished by the 12-month period, so that these patients had the same mean change rating as the group which did not receive LSD.

## Discussion

The results indicate that, as a group, patients treated with LSD showed more improvement than similar patients not so treated. Furthermore, the LSD patients who showed the greatest clinical improvement were those who displayed an insightful response during or within 24 hours of the single LSD treatment session. These patients, most of

Table 2.—FOLLOW-UP RESULTS

| Subject Group | Mean Ratings of Overall Change | |
|---|---|---|
| | At 6 mos | At 12 mos |
| LSD ($N = 20$) | 1.69 ± 0.39* | 1.94 ± 0.30 |
| No LSD ($N = 20$) | 0.82 ± 0.20 | 1.03 ± 0.20 |
| $p$ | $< .05$ | $< .02$ |
| LSD responders ($N = 8$) | 3.09 ± 0.45 | 2.51 ± 0.46 |
| LSD nonresponders ($N = 12$) | 0.76 ± 0.32 | 1.55 ± 0.38 |
| $p$ | $< .001$ | $< .02$ |
| | Change from 6 to 12 mos | |
| | Mean | p |
| LSD responders ($N = 8$) | —0.58 ± 0.27 | .10 |
| LSD nonresponders ($N = 12$) | 0.79 ± 0.19 | $< .01$ |
| No LSD ($N = 20$) | 0.21 ± 0.12 | .10 |

* Standard error of mean.

**Table 3.—COMPARISONS WITH RESPECT TO SOME BEHAVIOR AREAS**

| Behavior Area | Mean Rating of Change | |
|---|---|---|
| | 6 mos | 12 mos |
| A. Sexual* | | |
| LSD responders ($N = 6$) | 3.83 | 2.83 |
| LSD nonresponders ($N = 5$) | 2.00 | 2.00 |
| No LSD ($N = 11$) | 1.64 | 1.64 |
| B. Excessive alcohol or drugs | | |
| LSD responders ($N = 5$) | 2.80 | 2.40 |
| LSD nonresponders ($N = 4$) | 0.25 | 0.50 |
| No LSD ($N = 7$) | 0.00 | 0.00 |
| C. School, home or job performance | | |
| LSD responders ($N = 5$) | 3.20 | 1.60 |
| LSD nonresponders ($N = 8$) | 0.00 | 0.88 |
| No LSD ($N = 13$) | 1.08 | 1.62 |

* Homosexuality, frigidity, impotency, promiscuity.

whom had disorders of conduct, were initially diagnosed as psychopathic personalities with the Small structured interview (10). The findings suggest that Small's criteria for this diagnosis can be used to select candidates for LSD therapy. An immediate check on the adequacy of selection is provided by the LSD treatment session itself; for those patients who experience an insightful response can be expected to show relatively swift clinical improvement. Since only those patients who were 22 years of age or older showed insightful responses to LSD, age may also be an important variable.

Although results from the follow-up study clearly indicated that the LSD group showed more improvement than the matched control group, it seemed possible that the difference might be due to other forms of psychiatric treatment. That is, patients in the LSD group might also have had more follow-up treatment than control patients. When case records were examined to check this possibility, the results confirmed the opposite conclusion: three LSD cases had weekly psychotherapy in the year following treatment, but 13 control cases had weekly psychotherapy during this period.

It is of interest that the patients given LSD and classified as nonresponders tended to show significant improvement in a more gradual manner, so that they were rated as more improved at 12 months than at six months. In contrast, the LSD responders improved dramatically almost immediately but tended to show signs of relapse at a mean interval of about seven months following their LSD session.

Certain aspects of the study are clearly open to criticism, particularly the fact that the interviewer knew which patients had received LSD. It would be extremely difficult to avoid this problem, because of the distinctive effects of LSD. It can only be stated that the interviewer attempted to avoid interpretation of the ratings of change given by the patient and his relatives. Different clinical outcomes also could have resulted from differential motivation for treatment. However, this seems unlikely since ten patients of the LSD group were court-referred or had some legal problem relevant to hospital admission, such as threat of divorce; and similar legal problems were present in nine of the patients not treated with LSD. It is also obvious that the group was small and that any generalizations based on a small sample must viewed with great caution. However, similar findings have been obtained by other workers from different countries. For example, Johnsen (7) noted in his large series of cases that sexual perverts and psychopaths frequently had "deep emotional reactions with cosmic and mystic experiences" to LSD, whereas compulsive neurotics rarely reported such experiences.

Some LSD patients interviewed in the follow-up study indicated that they had recently begun to relapse and asked for additional treatment. One such case was a 25-year-old homosexual man who had achieved his first heterosexual intercourse six weeks after his LSD treatment and had managed to establish a relatively stable relationship with a woman until about eight months following this treatment. At this point he had begun to have homosexual fantasies once again and stopped dating. He was readmitted for another LSD treatment session, after which he felt that he had solved his problem. But he returned again after one month saying that he feared a relapse. He was readmitted once again for an additional treatment. At this time he stated that he was certain that his problem was solved. Following this third LSD session he left the hospital confident that he could maintain a heterosexual adjustment and he has succeeded in doing so for many months. Such cases suggest that follow-up contact after LSD treatment is desirable and that readmission for further sessions should be very seriously considered when there is impending relapse. It is noteworthy that most cases of relapse did not occur suddenly; as in the case cited, an interview would be likely to disclose the change in fantasy content which could be used as indication for further therapy.

It is also possible that a series of concentrated LSD sessions may yield results superior to those obtained with single treatments. In an LSD study currently in progress we have found several patients in whom insightful response appeared only with a second or third injection of LSD. In no case did a fourth treatment produce an insightful response when the first three had failed to elicit one.

Workers using LSD for psychotherapeutic purposes have frequently introduced adjunctive procedures, such as intensive psychotherapy and hypnosis (2) or sensory stimulation, such as music and pictures into the LSD sessions. We used no procedures of this kind. We deliberately refrained from interpretive comments, assumed a nondirective attitude, and allowed the patient to arrive at his own insights during the LSD sessions and subsequently. Despite this nondirective approach, the responses of the patients, *e.g.*, insights concerning their relationship to the world and realization of the need to respect other persons' dignity, were similar to those recorded by other observers using more forceful psychotherapeutic intervention (4). Many of our patients were motivated by external pressures to seek treatment for problem behavior, and, in our psychotherapeutic preparations for the LSD session attempts were made to define the behavior problem which required assistance. The working hypothesis underlying this approach is that *the probability of favorable behavioral change with LSD is increased in individuals in whom the behavior to be changed can be specified.* It follows that problems, such as homosexuality or consuming too much alcohol, might be more amenable to change than those which involve multiple activities and which can be described only in a general way, *e.g.,* passive-aggressive behavior. Our results support this expectation.

General personality assets of patients may also furnish prognostic cues for LSD treatment. Patients with good ego assets in spheres other than their personality deviation appeared to show more favorable change. The apparent relationship between favorable result and age may also be a function of the level of personality development.

It is important to emphasize that LSD treatments were administered to hospitalized patients under closely supervised conditions and that careful observation was maintained for at least 24 hours after the treatment. These conditions were instituted at the beginning of our work with LSD in accordance with a general attitude of caution and maximal safety. The necessity of such careful supervision is documented by recent reports of prolonged adverse reactions to LSD (5). Although careful selection of patients will, hopefully, minimize possible complications of LSD therapy, they can be recognized and dealt with only in a controlled setting. Furthermore, it seems possible that the supervised setting, designed to diminish the patient's anxiety as well as to promote safety, may be an essential condition for therapeutic benefit.

Several observations raise questions about the duration of LSD effects and their relation to the immediate response. The fact that the LSD-treated nonresponder group showed continuous improvement between six- and 12-month follow-ups raises the question, "Can one LSD experience facilitate personality growth over a long subsequent period of time, even though there is little immediate behavioral change?" The tendency of those who showed the greatest immediate behavioral change to relapse after several months gives the impression that, in some way, effects of the drug could have continued to be present for several months before they gradually disappeared. Observable neurophysiological changes produced by one dose of LSD in man are usually no longer evident after 24 hours (9). However, Adey *et al.* (1) observed some electrical effects lasting for about a week after LSD in the hippocampal regions of the cat, so that long-lasting functional changes in some brain areas seem quite possible.

Results to date support the view that immediate and subsequent reaction to LSD may be predicted from clinical observations and that the drug has favorable therapeutic benefits in a category of patients otherwise very difficult to treat. Further exploration of the use of LSD in treatment appears indicated; and research elucidating the mechanism of action of the drug should contribute in an important way to psychiatric pathophysiology.

## Summary

Twenty psychiatric patients treated with a single large dose of LSD were studied to determine degree of improvement in symptoms and problem behavior six months and one year after treatment. Clinical change in the LSD-treated group was compared with that in a patient group matched for age, sex, education, marital status, psychiatric diagnosis and clinical manifestations. The LSD group was divided into two groups: those displaying an immediate insightful response to LSD (responders) and those failing to do so (nonresponders). The responder group was found to consist mainly of patients with diagnoses of psychopathic personality and all were at least 22 years old.

Patients treated with LSD showed greater improvement than those in whom LSD was not used, even though two-thirds of the non-LSD group received systematic psychotherapy compared to only one-sixth of the LSD group. The LSD responders showed significantly more improvement than the LSD nonresponders. However, the responder group showed a tendency to relapse after six months, whereas the nonresponder group showed progressive improvement between six and 12 months.

It was concluded that patients with specific conduct disorders, who otherwise have reasonably well developed personality assets, are probably the most favorable candidates for LSD therapy. Although the probability of relapse is high after six months, successful retreatment has been demonstrated. Several possible shortcomings of the study, including the small number of cases, invite caution in interpretation of results, but they clearly encourage further study of the use of LSD in treatment.

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